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(56) References cited:
EP-A- 0 108 285
EP-A- 0 146 516
EP-A- 0 186 640
EP-A- 0 242 482
GB-A- 2 134 907
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Vol. 31, Jan. 1987, pages 76-80, G. ABELE et al.: "Inhibiting effect of (RS)-9-[4-hydroxy-2-hydroxymethyl)butyl]guanine on varicella-zoster virus replication in cell culture"

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Vol. 30, No. 4, Oct. 1986, pages 598-605, ALF LARSSON et al.: "Mode of action, toxicity, pharmacokinetics, and efficacy of some new antiherpesvirus guanosine analogs related to buciclovir"

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Description

Field of the invention

The present invention relates to novel and known chemical compounds and pharmaceutically acceptable salts thereof for use in therapy for therapeutic and prophylactic treatment of the acquired immuno deficiency syndrome (AIDS) and infections caused by viruses requiring reverse transcriptase for replication, such as human immunodeficiency viruses and hepatitis B viruses, and also for treatment of other virus diseases, such as those of herpes viruses, diseases which include both common infections and neoplastic diseases, i.e. cancer.

Background of the invention

The effects of viruses on bodily functions is the end result of changes occurring at the cellular and subcellular levels. The pathogenic changes at the cellular level are different for different combinations of viruses and host cells. While some viruses cause a general destruction (killing) of certain cells, other may transform cells into a neoplastic state.

Important common viral infections are herpes dermatitis (including herpes labialis), herpes keratitis, herpes genitalis, herpes zoster, herpes encephalitis, infectious mononucleosis and cytomegalovirus infections all of which are caused by viruses belonging to the herpes virus group. Other important viral diseases are influenza A and B which are caused by influenza A and B virus respectively. Another important common viral disease is viral hepatitis and especially hepatitis B virus infections are widely spread. Effective and selective antiviral agents are needed for treatment of these diseases as well as for other diseases caused by viruses.

Several different viruses of both DNA and RNA type have been shown to cause tumors in animals. The effect of cancerogenic chemicals can on animals result in activation of latent tumor viruses. It is possible that tumor viruses are involved in human tumors. The most likely human cases shown today are leukemias, sarcomas, breast carcinomas, Burkitt lymphomas, nasopharyngeal carcinomas and cervical cancers where RNA tumor viruses and herpes viruses are indicated. This makes the search for selective inhibitors of tumorogenic viruses and their functions an important undertaking in the efforts to treat cancer.

In the late seventies a new disease was reported, which subseqently was referred to as Acquired Immuno Deficiency Syndrome (AIDS). It is now generally accepted that a retrovirus referred to as HIV (Human Immunodeficiency Virus), formerly known as Human T-cell Lymphotropic Virus (HTLV-III) as Lymphadenopathy Associated Virus (LAV) plays an essential role in the etiology of AIDS. Different types of HIV have been found such as HIV-1 and HIV-2 and more are likely to be isolated.

AIDS is characterized by a profound immunodeficiency due to low numbers of a subset of lymphocyte-T-helper cells, which are one target for HIV-infection. The profound immunodeficiency in AIDS patients makes these patients highly susceptible to a variety of opportunistic infections of bacterial, fungal, protozoal or viral etiology. The etiological agents among viral opportunistic infections are often found in the herpes virus group, i.e. herpes simplex virus (HSV), Varicella Zoster virus (VZV), Epstein-Barr Virus (EBV) and, especially, cytomegalovirus (CMV). Other retroviruses affecting animals are feline leukemia virus and equine infectious anaemia virus. Human diseases such as multiple sclerosis, psoriasis and Kawasaki disease have also been reported to be associated with retrovirus infections.

Hepatitis B virus infections cause severe disease such as acute hepatitis, chronic hepatitis, fulminant hepatitis in a consider able number of persons. It is estimated that there are 200 million patients with chronic hepatitis B infection in the world. A considerable number of the chronic cases progress to liver cirrosis and liver tumours. In some cases the hepatitis infections are also take a rapid and severe course as in fulminant B hepatitis with about 90 % mortality. At present there is no known effective treatment against hepatitis B infections. The replication of hepatitis B virus is similar to that of retroviruses and it contains the same essential viral reverse transcriptase activity.

General outline of the invention

A great number of nucleoside analogues exhibit several antimetabolic activities. They do so by substituting for or competing with the naturally occuring nucleosides. Recently some nucleoside analogues have been described, which inhibit in cell culture the multiplication of human immunodeficiency virus (HIV, also called HTLV-III, LAV) the causative agent of AIDS and AIDS-related complex (ARC).

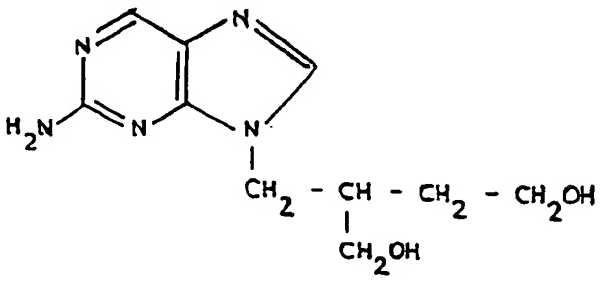
We have now found that activities for inhibition of HIV and/or herpes multiplication are exhibited by nucleoside analogues, in which the nucleoside bases are both natural and modified purine bases which in N-9 posi-

tion are derivatized with an acyclic side chain, branched in the 2'-position, and containing functional groups.

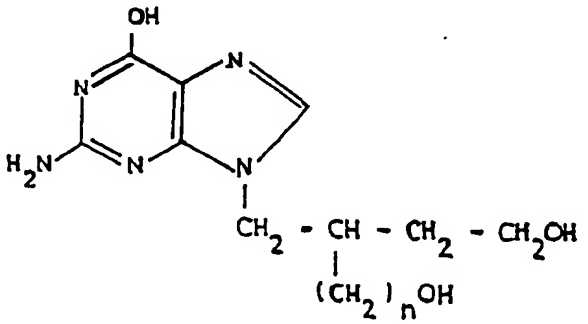
Prior Art

Purine derivatives with antiviral activity have previously been disclosed in the following references:
9-(Phosphonylmethoxyalkyl)adenines are described in AU-A-56328/86 and AU-A-56468/86;
9-(1,3-dihydroxy-2-propoxymethyl)purines and cyclic phosphate esters are described in US-A-4,565,868, US-A-4-590,269 and EP-A-184 473; and
9-(4-hydroxy-3-hydroxymethylbutyl)purine derivatives are described in EP-A-141 927.

In addition the compound of the formula



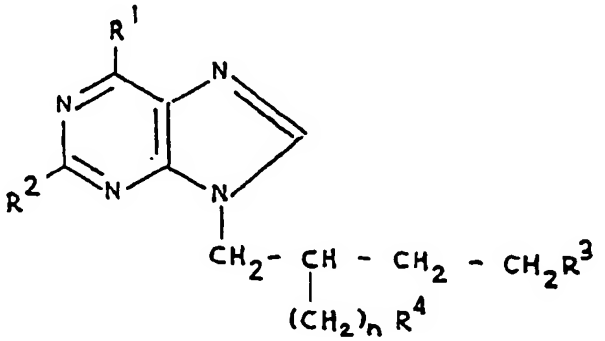
is known from EP-A-186 640;
and the compounds of the formula



wherein n = 1 or 2, are known from EP-A-146 516.

Disclosure of the invention

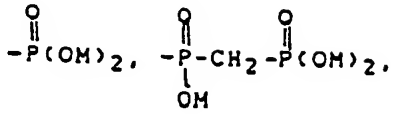
It has been found according to the present invention that the compounds of the formula



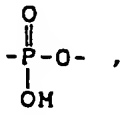
I

wherein:

R^1 is hydrogen, hydroxy, mercapto or amino;
R^2 is hydrogen, hydroxy, fluoro, chloro or amino;
R^3 and R^4 are independently selected from



amino, hydroxy
or an ether or ester residue thereof, or
R^3 together with R^4 is



wherein
M is hydrogen or a pharmaceutically acceptable counterion; and n is 1 or 2; and pharmaceutically acceptable salts thereof, inhibit the multiplication of human immunodeficiency virus (HIV). The compounds of the formula I are useful as therapeutic and/or prophylactic agents in the control and treatment of HIV virus infections in man.

In a more general aspect, the compounds of the formula I are useful as therapeutic and/or prophylactic agents in the control and treatment of infections caused by retroviruses and hepatitis B virus in mammals and man.

All retroviruses, including HIV, require the enzyme reverse transcriptase in their natural cycle of replication.

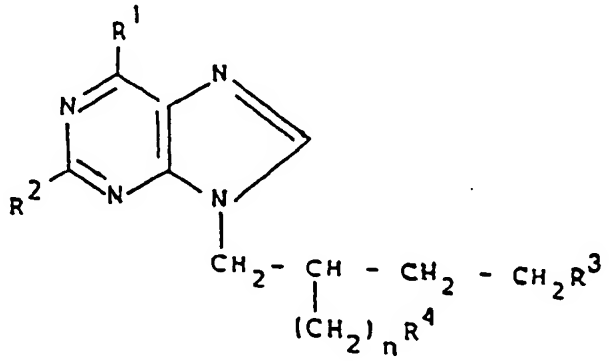
Hepatitis B virus (HBV) is a DNA virus with a unique circular double-stranded DNA genome which is partly single-stranded. It contains a specific DNA polymerase required for viral replication. This DNA polymerase also acts as a reverse transcriptase during the replication of HBV DNA via an RNA intermediate.

The compounds of the formula I inhibit the activity of reverse transcriptase of retroviruses including HIV as well as the activity of DNA polymerase of hepatitis B virus.

Another important area of use for the compounds of the formula I as in the treatment of herpes virus infections. Among the herpes viruses may be mentioned Herpes simplex type 1 and 2, varicella (Herpes Zoster), virus causing infections mononucleosis (i.e. Epstein-Barr virus) and cytomegalovirus. Important diseases caused by herpes viruses are herpes dermatitis (including herpes labialis), herpes genitalis, herpes keratitis, herpes encephalitis and herpes zoster.

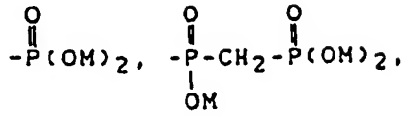
Another possible area of use for the compounds of the present invention is in the treatment of cancer and tumors, particularly those caused by viruses. This effect may be obtained in different ways, i.e. by inhibiting the transformation of virus-infected cells to a neoplastic state, by inhibiting the spread of viruses from transformed cells to other normal cells and by arresting the growth of virus-transformed cells.

The present invention relates to the use of a compounds of the formula I

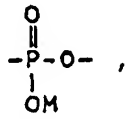


I

wherein:
R^1 is hydrogen, hydroxy, mercapto or amino;
R^2 is hydrogen, hydroxy, fluoro, chloro or amino;
R^3 and R^4 are independently selected from



amino, hydroxy
or an ether or ester residue thereof, or
R^3 together with R^4 is

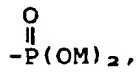


wherein
M is hydrogen or a pharmaceutically acceptable counterion; and n is 1 or 2; and pharmaceutically acceptable salts thereof for the manufacture of a medicament for therapeutic and/or prophylactic treatment of the acquired immuno deficiency syndrome and infections caused by viruses requiring reverse transcriptase for replication.

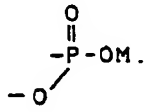
Preferably they can be used for the treatment of infections caused by HIV viruses or hepatitis B virus.

The compounds of the formula I contain one asymmetric center when $CH_2CH_2R^3$ and $(CH_2)_nR^4$ are different. Accordingly they exist in two optical forms which constitute a further aspect of the invention.

Preferred compounds to be used in accordance with the invention are those wherein R^1 and R^2 are independently hydrogen, hydroxy or amino and wherein R^3 is

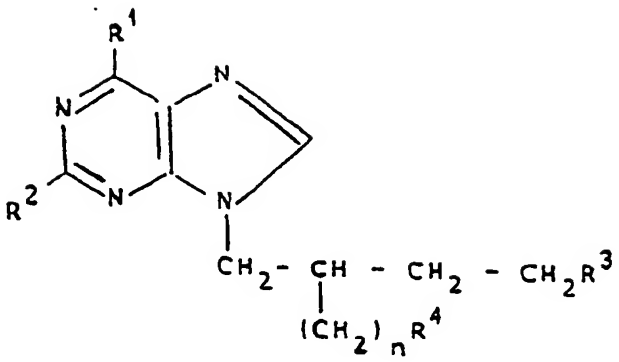


hydroxy or an ester derivative thereof, and R^4 is OH or an ester derivative thereof or wherein R^3 and R^4 together are



Preferably R^3 and R^4 are both hydroxy.

Examples of especially preferred compounds are those of the formula I

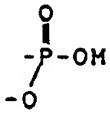


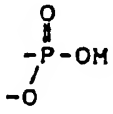
wherein

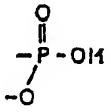
$R^1 = OH$, $R^2 = NH_2$, $R^3 = OH$, $R^4 = OH$

$R^1 = H$, $R^2 = NH_2$, $R^3 = OH$, $R^4 = OH$

$R^1 = NH_2$, $R^2 = H$, $R^3 = OH$, $R^4 = OH$

$R^1 = OH$, $R^2 = NH_2$, R^3 and R^4 = 

$R^1 = H$, $R^2 = NH_2$, R^3 and R^4 = 

$R^1 = NH_2$, $R^2 = H$, R^3 and R^4 = 

$R^1 = OH$, $R^2 = NH_2$, $R^3 = OCOC_{1-3}$, $R^4 = OCOC_{1-3}$

$R^1 = H$, $R^2 = NH_2$, $R^3 = OCOC_{1-3}$, $R^4 = OCOC_{1-3}$

$R^1 = NH_2$, $R^2 = H$, $R^3 = OCOC_{1-3}$, $R^4 = OCOC_{1-3}$

$R^1 = OH$, $R^2 = NH_2$, $R^3 = OCONH\text{-phenyl}$, $R^4 = OCONH\text{-phenyl}$

$R^1 = H$, $R^2 = NH_2$, $R^3 = OCONH\text{-phenyl}$, $R^4 = OCONH\text{-phenyl}$

$R^1 = NH_2$, $R^2 = H$, $R^3 = OCONH\text{-phenyl}$, $R^4 = OCONH\text{-phenyl}$

Esters and ethers of the purine derivatives are also included in the invention. Examples of esters are phosphate esters, carboxylic esters, carbonate esters, carbamate esters or sulphonic esters. The acid part of the esters may have alkyl, aryl or arylalkyl chains, where the aryl functionalities are optionally substituted for example by alkoxy, amino, nitrile, alkyl or sulphonamido groups or by one or more halogen atoms.

Examples of other types of derivatives of the purine bases are alkyl or arylalkyl derivatives of the primary hydroxyl group(s). The arylalkyl ether derivatives may be for example benzyl or triphenyl methyl and the aryl moiety may be optionally substituted. Furthermore, it is understood that the examples of the pharmaceutically acceptable salts cited below also apply to the various esters or derivatives of the purine bases of the invention.

In a compound of the formula I R^3 and R^4 as an ether residue can be defined as OR^5, wherein R^5 is C_{1-6} alkyl, arylalkyl optionally substituted with one or more alkoxy, amino, nitrile or sulphamido groups or one or more

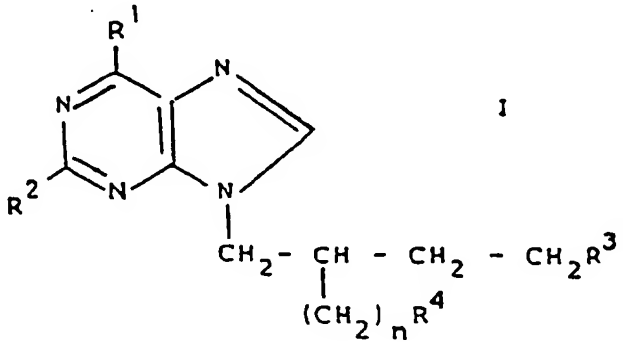
halogen atoms.

R^3 and R^4 as an ester residue can be derived from a carboxylic acid R^6COOH, a carbonic acid R^7OCOOH, a double ester of a carbonic acid $R^7CO_2CH(R^8)OCO_2H$, a sulphonic acid R^7SO_2OH, a carbamic acid $R^7NHCOOH$ or a phosphoric acid, wherein R^6 is hydrogen, C_{1-17} alkyl, alkoxyalkyl, arylalkyl or aryl, R^7 is C_{1-17} alkyl, arylalkyl or aryl, R^8 is hydrogen or C_{1-3} alkyl and said aryl and arylalkyl groups optionally can be substituted with one or more alkyl, alkoxy, amino, nitrile, sulphonamide groups or one or more halogen atoms.

Examples of pharmaceutically acceptable salts of the compounds of formula I include base salts, e.g. derived from an appropriate base, such as alkali metal (e.g. sodium, potassium, alkaline earth metal (e.g. magnesium) salts, ammonium and NX_4^+ (wherein X is C_{1-4} alkyl). Physiologically acceptable acid salts include salts of inorganic carboxylic acids such as acetic, lactic, gluconic, citric, tartaric, maleic, malic, pantothenic, isethionic, oxalic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic, p-chlorobenzenesulphonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, hydroiodic, sulfuric, phosphoric and sulfamic acids.

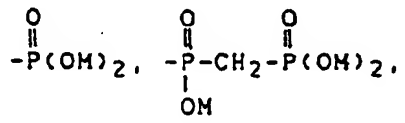
Physiologically acceptable counterions of the phosphonate groups include inorganic and organic counterions. Inorganic counterions are for example ammonium, sodium, potassium, lithium, magnesium and calcium. Organic counterions are derived from non-toxic bases, such as primary, secondary and tertiary amines, including naturally occuring amines. Examples of such amines are diethylamine, triethylamine, isopropylamine, ethanolamine, morpholine, 2-diethylaminoethanol, glucosamine, N-methylglucamine, piperazine and dicyclohexylamine.

The present invention also relates to novel compounds of the formula

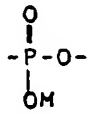


I

wherein:
R^1 is hydrogen, hydroxy, mercapto or amino;
R^2 is hydrogen, hydroxy, fluoro, chloro or amino;
R^3 and R^4 are independently selected from



amino, hydroxy
or an ether or ester residue thereof, or
R^3 together with R^4 is



wherein
M is hydrogen or a pharmaceutically acceptable counterion; and n is 1 or 2; with the proviso that, when R^2 is

amino and R^3 and R^4 are hydroxy, R^1 is not hydroxy and in addition, when n = 1, R^1 is not hydrogen, and pharmaceutically acceptable salts thereof.

The invention furthermore provides:

A pharmaceutical composition comprising a new compound of the formula I as active ingredient; and

A method for therapeutic and/or prophylactic treatment of virus infections in an aminal or human host in need of treatment comprising administering an effective amount of a new compound of the formula I.

It is a preferred aspect of the invention to treat infections caused by herpes virus or a virus requiring reverse transcriptase for replication, including human immuno deficiency viruses and hepatitis B virus.

In clinical practice the purine derivatives of the formula I will normally be administered orally, by injection or by infusion in the form of a pharmaceutical preparation comprising the active ingredient in the form of the original compound or optionally in the form of a pharmaceutically acceptable carrier which may be a solid, semi-sold or liquid diluent or an ingestible capsule. The compound may also be used without carrier material. As examples of pharmaceutical preparations may be mentioned tablets, dragées, capsules, granulates, suspensions, elixirs, syrups, solutions etc. Usually the active substance will comprise between 0.05 and 20 % for preparations intended for injection and between 10 and 90 % for preparations intended for oral administration.

In the treatment of patients suffering from retrovirus, especially HIV, or hepatitis B virus infections, it will be preferred to administer the compounds by any suitable route including the oral, parenteral, rectal, nasal, topical and vaginal route. The parenteral route includes subcutaneous, intramuscular and intravenous administration. The topical route includes buccal and sublingual administration. The dosage at which the active ingredients are administered may vary within a wide range and will depend on various factors such as the severity of the infection, the age of patient etc., and may have to be individually adjusted. As a possible range for the amount of the compounds of the invention or a physiologically acceptable salt thereof to be administered per day may be mentioned from about 10 mg to about 10 000 mg, preferentially 100-500 mg for intravenous administration and preferentially 100-3000 mg for oral administration.

Compounds of the formula I can cooperate synergistically or additively with a wide range of other therapeutic agents, thereby enhancing the therapeutic potential of both agents without adding the toxic effects, thus increasing the therapeutic ratio.

Therefore, a compound of formula I or a pharmaceutically acceptable derivative thereof can be used in combination therapy, wherein the two active agents are present in a ratio resulting in an optimal therapeutic ratio. This can be provided either by a synergistic effect against the viral infection and/or by a decrease in toxicity while maintaining a therapeutic effect which is additive or synergistic.

The optimal therapeutic ratio is observed when the two agents are present in a ratio of 500:1 to 1:500, preferably 100:1 to 1:100, particularly 20:1 to 1:20 and especially 10:1 to 1:10.

Said combinations may conveniently be administered together, for example, in a unitary pharmaceutical formulation, or separately for example as a combination of tablets and injections administered at the same time or different times, in order to achieve the required therapeutic effect.

The compounds of the formula I are potentiated by interferons, other antiviral agents such as foscarnet, AZT, HIV protease inhibitors, immunomodulators, interferon inducers and growth factors.

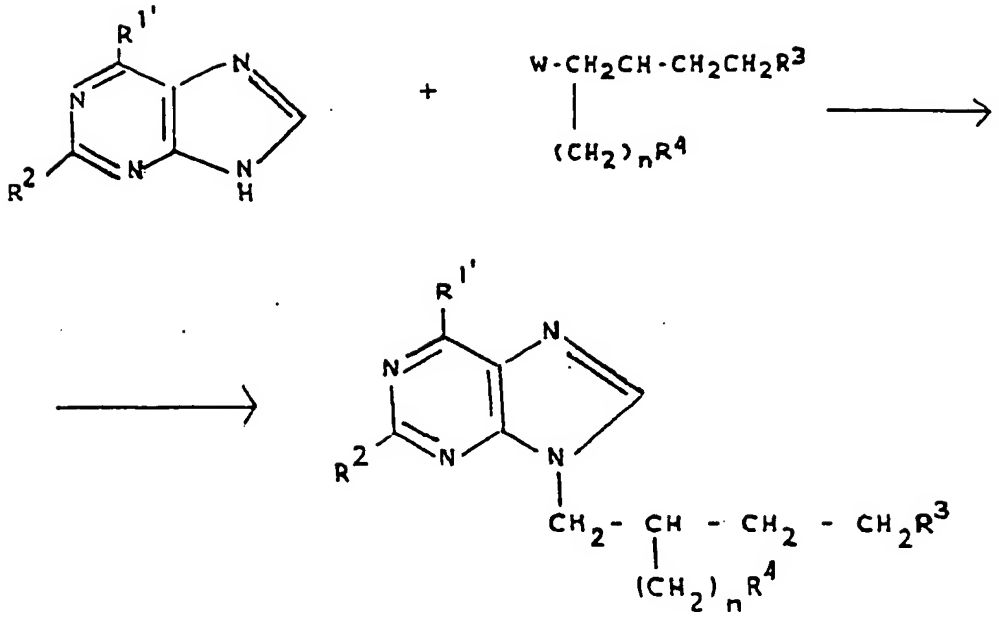
Particularly preferred types of interferon are α, β and γ and interferon inducers such as "Ampligen" (Hem Research).

Other combinations suitable for use according to the present invention include those wherein the second agent is, for example, interleukin II, suramin, foscarnet or an ester thereof, HPA 23, inhibitors of HIV protease such as pepstatin, steroids, medications such as levamisol or thymosin to increase lymphocyte numbers and/or function as appropriate, or GM-CSF and other factors regulating cell functions.

Methods of preparation

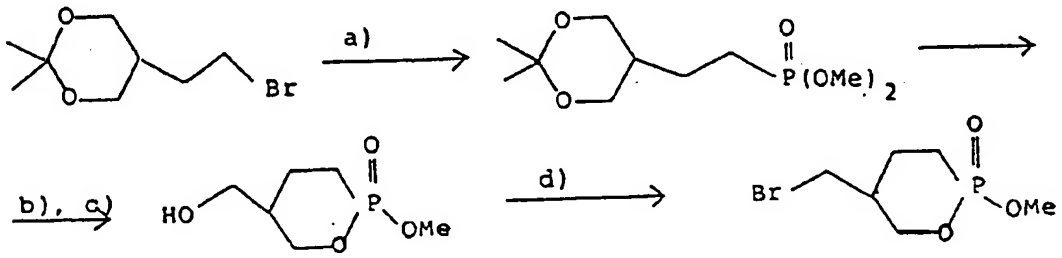
The compounds of the invention may be prepared by one of the following general methods, constituting a further aspect of the invention.

A. Condensing an acyclic side chain as comprised in formula I, to the N-9 position of a purine derivative. The acyclic side chain has a terminal leaving group and the functional groups may be optionally protected with known groups used for protection of hydroxy, amino or phosphonate functions.



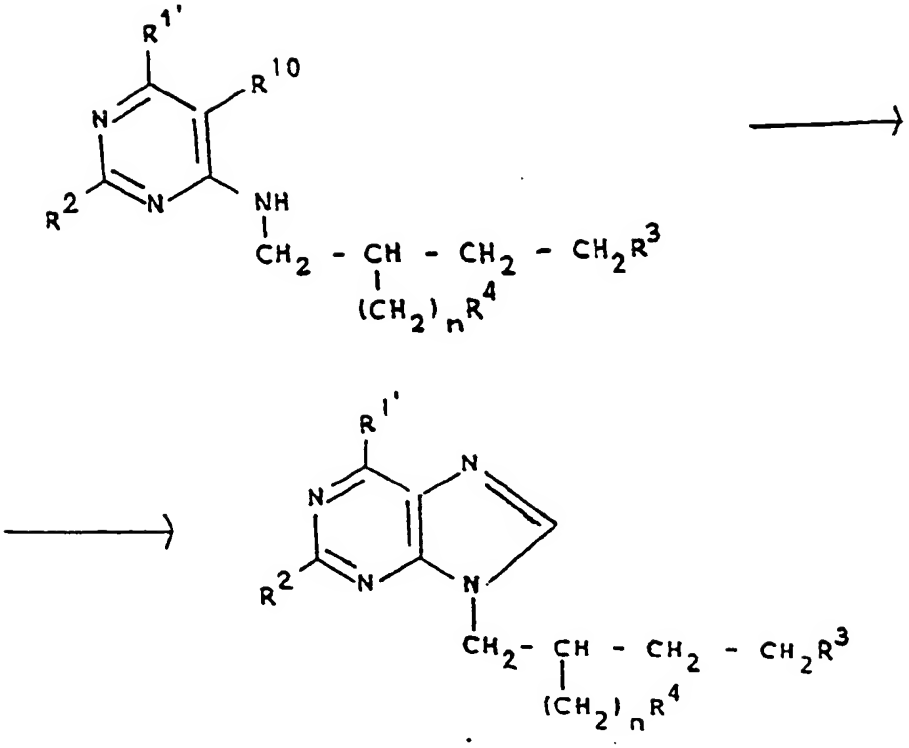
Examples of suitable derivatives of the reacting species are those wherein $R^{1'}$ is Cl, or R^1 as defined above, R^1, R^2, R^3, R^4 and n are as defined above, and W is a suitable leaving groups, such as Cl, Br, J, alkyl or aryl sulfonyloxy, trifluoromethanesulfonyloxy. The condensation reaction is performed in an organic soluent such as dimethyl formamide, dimethylsulfoxyde, ethanol, acetonitrile, dichloromethane or the like at a temperature of between 0°C and 150°C for 1 hour to 5 days, and after condensation the products may be hydrolyzed or converted by conventional methods, known to those skilled in the art, into compounds of the formula I.

For the case of a phosphonate the side chains condensed to a purine base could be prepared in different ways. One example is the following reaction sequence, where the starting material 5-(2-bromoethyl)-2,2-dimethyl-1,3-dioxane has been described (M.R. Harnden and R.L. Jarvest, Tetrahedron Letters, Vol. 26, pages 4265-4268, 1985).



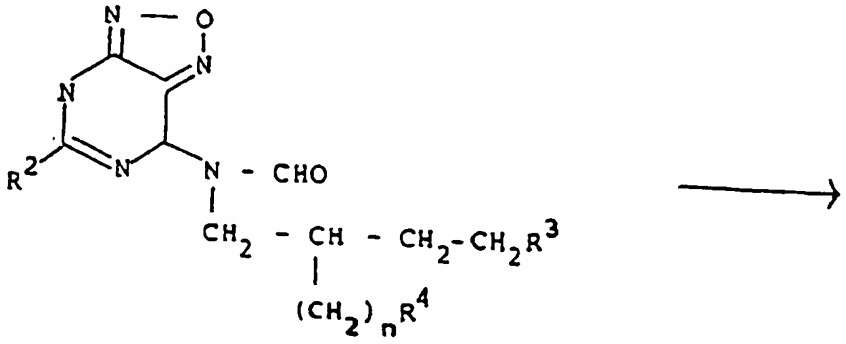
a) $P(OMe)_3$; B) H^+, MeOH; c) MeO-; d) N-bromosuccinimide, triphenylphosphine;

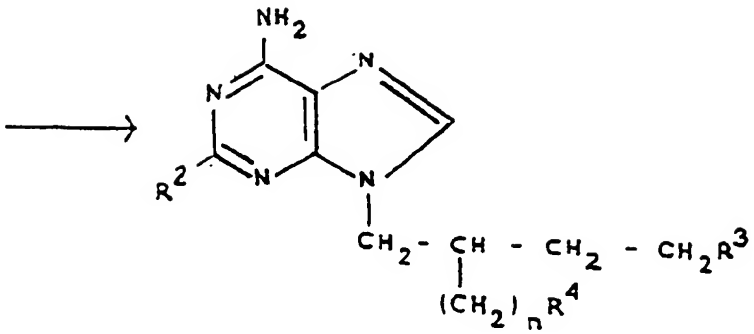
B. Imidazole ring closure of a substituted pyrimidine derivative to the purine base followed by removal of the protecting groups.



R^1, R^2, R^3 and R^4 are as defined above, R^{10} is nitroso, nitro, amino or an amino derivative such as formylamino or orthoesteramino. The ring closure may be performed by known methods (the principles which are given for example by E. Lunt in Comprehensive Organic Chemistry (Eds. D. Barton and W.B. Ollis, Pergamon Press 1979) vol 4, p. 499-505 and by G. Shaw in Comprehensinve Heterocyclic Chemistry (Eds. A.R. Katritzsky and C.W. Reese, Pergamon Press 1984) vol. 5, p. 570-573. The reaction may be performed in an organic solvent such as for example, formic acid, formamide, orthoformate ester or diethoxymethylacetate at a temperature from 25°C to 250°C for 10 minutes to 24 hours. When R^{10} is nitroso or nitro, these groups first have to be reduced to an amino group by any known method.

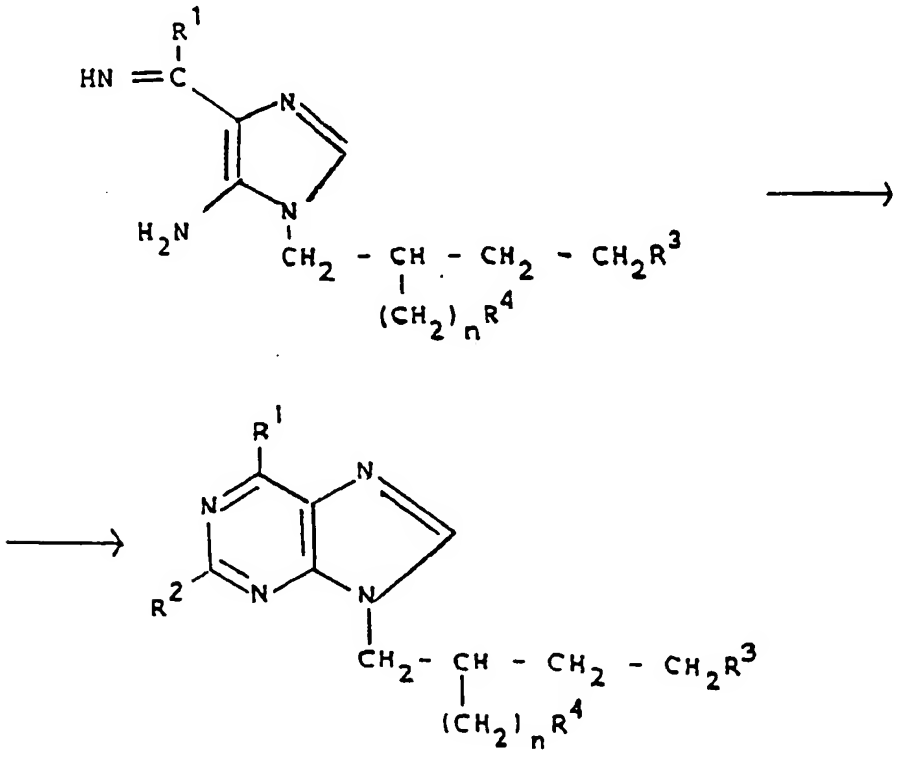
C. Imidazole ring closure via a furazano[3,4-d]pyrimidine ring system to the purine base followed by removal of the protecting groups.





R^2, R^3 and R^4 are as defined above. The ring closure may be performed by heating following reductive cleavage of the furazane ring by for example zink in acetic acid. After reaction the 6-NH_2 group of the purine may optionally be transformed to a hydroxy group by treatment with for example sodium nitrile in acetic acid.

D. Pyrimidine ring closure to the purine base followed by removal of the protecting groups.

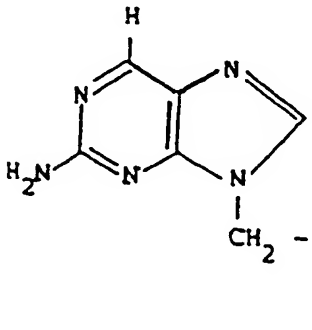


The ring closure may be performed according to known methods which have been described for example by G. Shaw in Comprehensive Heterocyclic Chemistry (Eds. A.R. Katritzsky and C.W. Reese, Pergamon Press 1984) Vol. 5, p. 583-591 and by E. Lunt in Comprehensive Organic Chemistry (Eds. D. Barton and W.B. Ollis, Pergamon Press 1979) Vol. 4, p. 505-508.

The described methods A-D may be used to give mixtures of optical isomers, or in appropriate cases a single optical isomer. A compound according to the invention in the form of an optical isomer can be prepared if in method A either an optically active acyclic side chain is condensed to the N-9 position of the purine derivative or the condensation is directed to the formation of an optical isomer by means of another optically active compound, and in methods B-D starting materials having an optically active side chain are subjected to the ring closure. Additionally a single optical isomer may be obtained from the racemic mixtures by methods known per se.

The following examples will further illustrate the invention.

Example 1 2-(2-Aminopurin-9-yl)methylbutane-1,4-diol



VSB 212

To a solution of crude dimethyl (2-aminopurin-9-ylmethyl)succinate (3.2 g, 10.9 mmol), dissolved in tert. butanol (250 ml) at 40°C, was added lithium borohydride (1.3 g, 60 mmol) in portions with stirring. After 1 hour at ambient temperature, water (30 ml) was added slowly and stirring continued over night. Inorganic salts were filtered and the solution evaporated to dryness. Yield of crude product was 1.6 g (50 %). Chromatography on silica (chloroform + methanol 7+1) afforded pure product.

^{1}H NMR (DMSO-d_6) : δ 31.4 (m, 2H) CH_2CH_2OH; 2.14 (m, 1H) CH; 3.33 (d, 2H) CH-CH_2OH; 3.44 (diffuse q, 2H); 4.05 (AB part of ABX, 2H) N-CH_2; 6.37 (broad s, 2H) NH_2; 7.99 (s, 1H) H8; 8.56 (s, 1H) H6.

^{13}C NMR (D_2O): δ 33.11 CH_2CH_2OH; 39.58 CH; 46.34 NCH_2; 61.35 and 63.51 2xCH_2OH; 128.41 C5; 146.92 C8; 150.48 C6; 155.05 C4; 161.50 C2.

The starting material dimethyl 2-(2-aminopurin-9-ylmethyl)succinate was prepared as follows (a,b):

a) Dimethyl 2-(2-amino-6-chloropurin-9-ylmethyl)succinate

A mixture of 2-amino-6-chloropurine (4.07 g, 0.024 mol), dimethyl itaconate (5.00 g, 0.032 mol), and sodium hydride (55 % in oil, 0.2 g) in 50 ml of dry dimethylformamide was stirred at room temperature for 3 days. About 50 ml of water was added and the mixture was washed with n-hexane (2x50 ml) and then extracted with 2x50 ml of dichloromethane. The combined CH_2Cl_2 extracts were washed with 2x20 ml of water, dried with magnesium sulfate, and evaporated in vacuum. Treatment with ether and drying afforded a white crystalline product. Chromatograpy (silica gel, chloroform + methanol 15+1) yielded 5.54 g (71 %) or recrystallization (MeOH-H_2O) yielded 5.15 g (66.1 %) of dimethyl 2-(2-amino-6-chloropurin-9-ylmethyl)succinate.

UV spectrum in EtOH, λ max (nm): 310 (247).

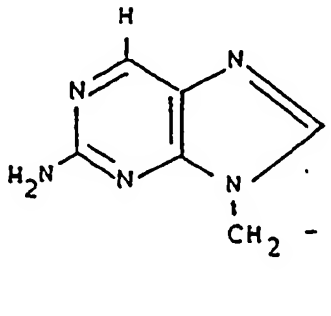
^{1}NMR ($CDCl_3$) δ 2.67 (dd, 2H) CH_2COO; 3.46 (m, 1H) CH; 3.70 (2s, 2x3H) OCH_3; 4.42 (ABX system, Jgem = 14 Hz, 2H) NCH_2; 5.35 (broad s, 2H) NH_2; 7.79 (s, 1H) H8.

b) Dimethyl 2-(2-aminopurin-9-ylmethyl)succinate

A mixture of dimethyl 2-(2-amino-6-chloropurin-9-ylmethyl)succinate (3.28 g, 10 mmol), sodium acetate (1.5 g) and 5 % palladium on charcoal (0.4 g) in ethanol (200 ml) was hydrogenated with agitation in a Parr apparatus at 40 psi for 115 h/room temperature. After filtration, sodium acetate (1.6 g) and 5 % Pd/C (0.4 g) were added and the hydrogenation was continued for 70 h. After filtration and evaporation to dryness, the residue was extracted with 2x50 ml of chloroform and the combined extracts were evaporated to dryness affording 2.6 g (89 %) of crude dechlorinated product.

^{1}H NMR (DMSO-d_6) δ 8.00 (s, 1H) H8; 8.56 (s, 1H) H6.

Example 2 2-(2-Aminopurin-9-yl)methylbutane-1,4-diol diacetate



VSC 610

A mixture of 4-acetoxy-2-bromomethylbutyl acetate (0.465 g, 1.74 mmol), 2-aminopurine (0.282 g, 2.09 mmol), and powdered potassium carbonate (1.20 g, 8.70 mmol) in N,N-dimethylformamide (20 ml) was stirred at room temperature for 5 days. Chloroform (40 ml) was added, solid material was removed by filtration, and the solution was evaporated in vacuum to small volume. Chromatography on 50 g SiO_2 with chloroform + methanol (7+1) as eluent gave a fraction 70-130 ml, which was evaporated and dried in vacuum, finally at 0.1 mBar to give 0.349 g (62 %) of 2-(2-aminopurin-9-yl)methylbutane-1,4-diol diacetate. TLC on silica (chloroform + methanol 7+1): R_f 0.57.

^{1}H NMR ($CDCl_3$+CD_3OD); δ 8.64 s, 1H) H6; 7.92 (s, 1H) H8; 5.82 (broad s, 2H) NH_2; 4.3-4.15 (m, 4H) 2 CH_2OAc; 4.33 (d, 2H) CH_2N; 2.50 (m, 1H) CH; 2.06 (s, 6H) 2 CH_3COO; 1.75 (q, 2H) $C\underline{H}_2CH_2OAc$;^{13}C NMR ($CDCl_3$+CD_3CD): δ 170.96, 170.66 (2 C=O); 159.89 (C2); 153.13 (C4); 148.77 (C6); 142.84 (C8); 126.83 (C5) 63.78 ($CHCH_2$-OAc); 61.47 ($CH_2\underline{C}H_2OAc$); 44.05 (CH_2N); 35.15 (CH); 27.59 ($\underline{C}H_2CH_2O$); 20.22, 20.05 (2 CH_3). The starting materials were prepared by the following sequence of reactions (a-e):

a) α-Trityloxymethyl-γ-butyrolactone

A mixture of α-hydroxymethyl-γ-butyrolactone (26.83 g, 0231 mol) (G. Claeson and H.-G. Jonsson, Arkiv för Kemi 28, 167 (1967)), trityl chloride (77.3 g, 0.277 mol) and dry pyridine (200 ml) was stirred at room temperature for a few hours until homogeneous. After 10 days at room temperature the solution was poured into a mixture of 500 ml water and 500 ml n-hexane. The precipitate was washed with water and hexane and dried finally at 0.1 mBar to give 65.60 g (79 %) of crude product, contaminated with some trityl alcohol. TLC on silica (ethyl acetate + n-hexane 1+3): R_f 0.38.

^{13}C NMR ($CDCl_3$): δ 177.84 (C=0); 143.71, 128.68, 127.96 and 127.20 (phenyl); 86.96 (O $\underline{C}PH_3$); 67.26 ($\underline{C}H_2OCO$); 62.49 ($\underline{C}H_2OTr$); 40.31 (CH); 26.15 ($\underline{C}H_2CH_2O$).

b) 2-Trityloxymethyl-1,4-butanediol

α-Trityloxymetyl-γ-butyrolactone (60.21 g, 0.168 mol) was added in small portions to a stirred suspension of lithium aluminium hydride (9.53 g, 0.251 mol) in dry tetrahydrofuran (300 ml) and the mixture was refluxed for 1 h. Slow addition of 10 ml H_2O + 10 ml 15 % NaOH and 30 ml H_2O produced a white sandy precipitation which was filtered off and washed with 2x50 ml tetrahydrofuran. The filtrate was evaporated to a small volume and dissolved in diethyl ether (300 ml), silica gel (250 g) was added and the mixture was carefully evaporated to a homogeneous powder. In a chromatography column the crude product - silica gel mixture was placed on top of silica gel (250 g) in n-hexane. Eluting with ethyl acetate + n-hexane (1+3), 2200 ml, removed trityl alcohol. Further eluting with ethyl acetate + ethanol (9+1) gave fractions 2900-3700 ml (from start), which after evaporation in vacuum produced a crystallizing oil. Yield 52.77 g (87 %). TLC on silica: ethyl acetate + n-hexane (1+3), R_f 0.05; ethyl acetate + ethanol (9+1), R_f 0.81.

c) 2-Trityloxymethyl-1,4-butanediol diacetate

To a stirred mixture of 2-trityloxymethyl-1,4-butandiol (50.85 g, 0.140 mol) and triethylamine (42.6, 0.42 mol) in dry diethyl ether (500 ml) was added slowly a solution of acetyl chloride (27.5 g, 0.35 mol) in ether (25 ml) with external cooling with cold water to maintain room temperature in the mixture. After 45 min the triethylamine hydrochloride was filtered off and washed with a little ether. The combined filtrate was washed with water (50 ml), 0.5 M hydrochloric acid (100 ml) and water (50 ml), dried with magnesium sulfate and evapo-

rated in vacuum, finally at 0.1 mBar, to give 61.03 g (97 %) of crude oily product. TLC on silica (ethyl acetate + n-hexane 1+1): R_f 0.68.

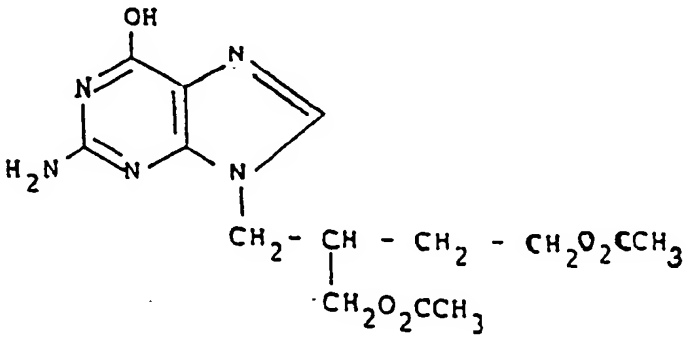
d) 4-Acetoxy-2-hydroxymethylbutyl acetate

2-Trityloxymethyl-1,4-butanediol diacetate (60.90 g, 0.136 mol) was dissolved in acetic acid (320 ml) at 100°C and water, (80 ml) was added. The solution was kept at 100°C for 15 min, evaporated in vacuum to small volume and cooled to 0°C. The precipitate was filtered off and washed with cold ethyl acetate to give 26.44 g (theory 35.51 g) of tritylalcohol. The combined filtrate was evaporated to small volume. The compound was purified on a silica gel column (500 g SiO_2); eluent 0-2700 ml ethyl acetate + n-hexane (1+1), 2700-3740 ml ethyl acetate + n-hexane (2+1), then neat ethyl acetate. The fractions 2540-4800 ml were evaporated to give 14.20 g (51 %) of pure 4-acetoxy-2-hydroxy-methylbutyl acetate. TLC on silica (ethyl acetate + n-hexane 1+1): R_f 0.30.
^{13}C NMR ($CDCl_3$): δ 171.08, 170.88 (2 C=O); 64.07 (CH_2OH); 62.10, 61.45 (2 CH_2OAc); 37.07 (CH); 26.76 ($\underline{C}H_2CH_2OAc$); 20.39 (2 CH_3).

e) 4-Acetoxy-2-bromomethylbutyl acetate

A solution of 4-acetoxy-2-hydroxymethylbutyl acetate (11.04 g, 0.054 mol) and triphenylphospine (21.27 g, 0.081 mol) in dry dichloro methane (150 ml) was stirred at 0°C, and N-bromo-succinimide (14.43 g, 0.081 mol) was added in portions. The mixture was kept at 0°C for 20 h, evaporated to small volume and stirred with 50 ml of ethyl acetate + n-hexane (1+1). The white triphenylphosphine oxide was filtered off and washed with a little ethyl acetate + n-hexane (1-1). The combined filtrate was evaporated and purified on a 200 g SiO_2 column with ethyl acetate + n-hexane (1+1) as eluent. The 250-550 ml fraction was evaporated in vacuum to give 11.90 g (82 %) of pure 4-acetoxy-2-bromomethylbutyl acetate. TLC on silica (ethyl acetate + n-hexane 1+1): R_f 0.59.
^1H NMR ($CDCl_3$): δ 4.2-4.0 (m, 4H) 2 CH_2OAc; 3.53 (ABX system, 2H) CH_2Br; 2.25-2.1 (m, 1H) CH; 2.08, 2.06 (2 s, 2x3H) 2 $COCH_3$; 1.79 (m, 2H) $C\underline{H}_2CH_2OAc$.
^{13}C NMR ($CDCl_3$): δ 170.91, 170.74 (2 C=O); 64.90 ($CH\underline{C}H_2OAc$); 61.71 ($CH_2\underline{C}H_2OAc$); 36.56 (CH); 34.74 (CH_2Br); 28.88 (CH_2CH_2O); 20.95 ($2CH_3$).

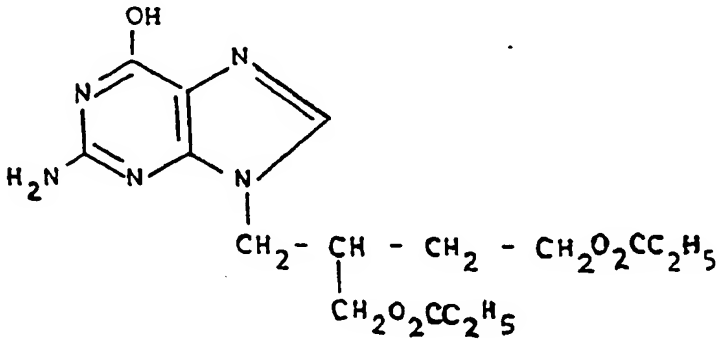
Example 3 9-(4-Acetoxy-2-acetoxymethylbutyl)guanine [2-(guanin-9-ylmethyl)-1,4-butanediol diacetate]



VSA 639

A mixture of 9-(4-hydroxy-2-hydroxymethylbutyl)guanine (0.50 g, 2.0 mmol), acetic anhydride (1.02 g, 10.0 mmol), pyridine (1.11 g, 14.0 mmol), and dry N,N-dimethylformamide (25 ml) was stirred at room temperature for 13 days and then evaporated to dryness in vacuum. The crystalline residue was heated with 10 ml of water and lyophilized and recrystallized from water to give 0.468 g (69 %) of 9-(4-acetoxy-2-acetoxymethylbutyl)guanine.
^{13}C NMR ($CDCl_3$+CD_3OD): δ 64.15 ($CH\underline{C}H_2O$); 61.98 ($CH_2\underline{C}H_2O$); 44.71 (CH_2N); 35.88 (CH); 27.95 ($\underline{C}H_2CH_2O$); 20.87, 20.68 (2 CH_3).

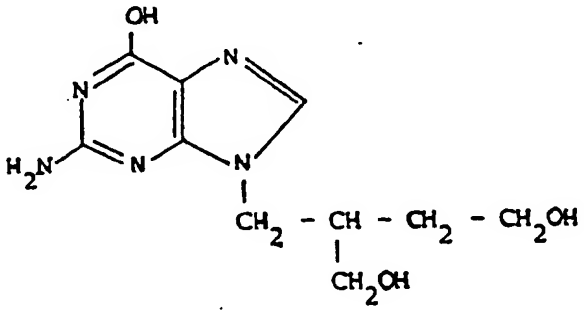
Example 4 9-(4 Propionoxy-2-propionoxymethylbutyl)guanine [2-(guanin-9-ylmethyl)-1,4-butanediol dipropionate]



VSC 637

A mixture of 9-(4-hydroxy-2-hydroxymethylbutyl)guanine (0.50 g, 2.0 mmol), propionic anhydride (1.56 g, 12.0 mmol), pyridine (1.27 g, 16.0 mmol), and dry N,N-dimethylformamide (25 ml) was stirred at room temperature for 14 days and then evaporated to dryness in vacuum. The crystalline residue was heated with 10 ml of water and lyophilized and recrystallized from water to give 0.418 g (57 %) of 9-(4-propionoxy-2-propionoxymethylbutyl)-guanine.
^{13}C NMR ($CDCl_3$+CD_3OD): δ 64.00 ($CH\underline{C}H_2O$); 61.86 $CH_2\underline{C}H_2O$); 44.78 (CH_2N); 35.95 (CH); 28.00 ($\underline{C}H_2CH_2O$); 27.56, 27.44 (2 $CH_3\underline{C}H_2CO$); 9.00 (2 CH_3).

Example 5 (-)-9-(4-Hydroxy-2-hydroxymethylbutyl)guanine



VSB 647

A solution of (-)-2-(2-amino-6-chlorpurin-9-ylmethyl)-1,4-butanediol (11.5 mg, 0.0423 mmol) in 50 % aqueous formic acid (0.75 ml) was kept at 100°C/2 h and then evaporated to dryness, dissolved in 2 ml of water and lyophilized. The product was dissolved in 1 ml of water, 2 drops of conc. aqueous ammonia was added and the solution kept at 100°C for 10 min, flushed with nitrogen to remove ammonia, and lyophilized. The residue was dissolved by warming with 1.2 ml of 20 % aqueous methanol and the solution filtered and kept in open air to allow for slow partial evaporization of solvent. Crystalline needles were formed. Filtration, washing with 3 drops of water and drying yielded 6.4 mg (60 %) of (-)-9-(4-hydroxy-2-hydroxymethylbutyl)guanine.

The compound was found to be levorotatory (ethanol, 589 and 546 nm). It produced a proton NMR (DMSO-d_6) identical to that of the racemate. TLC on silica (ethyl acetate + methanol + water 7+2+1): R_f 0.37, identical to that of the racemate.

The starting material was prepared as follows (a-b):

a) (-)-Dimethyl-2-(2-amino-6-chloropurin-9-ylmethyl)succinate

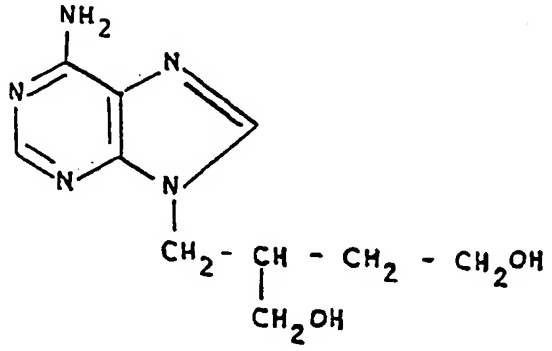
The racemic compound was resolved by repeated chromatography on a microcrystalline triacetylcellulose column, (Perstorp Biochem, Lund, Sweden) with 95 % ethanol as mobile phase. The slower moving (-)-enantiomer produced a proton NMR spectrum identical to that of the racemic compound (±). The resolution was followed by proton NMR in deuterochloroform at 200 MHz with tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]-europium(III) as chiral shift reagent. By addition of 1-1.5 parts (per weight) of shift reagent, the methyl ester signal of the racemate (2 close singlets at 3.69 and

3.695 ppm) were split into one base-line separated low-field pair (low-field signal from the (+)-enantiomer high-field signal from the (-)-enantiomer) and one less resolved high-field pair. The enantiomeric excess was then calculated from the ratio of the low-field signals.

b) (-)-2-(2-Amino-6-chloropurin-9-ylmethyl)-1,4-butanediol

To a solution of (-)-dimethyl-2-(2-amino-6-chloropurin-9-ylmethyl)succinate (enantiomeric excess 85 %; 19.9 mg, 0.0607 mmol), dissolved in tert. butanol (2.0 ml) at 40°C, was added lithium borohydride (30 mg, 1.38 mmol) in portions with stirring. After 1 h at ambient temperature, water (0.3 ml) was added slowly and stirring continued over night. Inorganic salts were filtered, washed carefully with tert. butanol and the solution was evaporated to dryness. Preparative thin-layer chromatography (PSC-Fertigplatten, Merck) with chloroform + methanol (5+1) as mobile phase afforded 16.5 mg (theoretical yield) of (-)-2-(2-amino-6-chloropurin-9-ylmethyl)-1,4-butanediol. $[\alpha]_D^{20}$ - 5.20°, $[\alpha]_{546}^{20}$ - 5.92° (c 0.625, ethanol). TLC on silica (chloroform + methanol 5+1): R_f 0.40, identical to that of the racemate.

Example 6 9-(4-Hydroxy-2-hydroxymethylbutyl)adenine



VSC 600

Dimethyl 2-(adenine-9-ylmethyl)succinate (2.93 g, 0.010 mol) was dissolved by warming with tert. butanol (120 ml), lithium borohydride (1.10 g, 0.05 mol) was added in portions and the mixture was stirred at ambient temperature for 3 h, water (10 ml) was added and stirring was continued over night. Inorganic material was filtered off and washed with tert. butanol and the filtrate evaporated to small volume. Chromatography on silica (ethyl acetate + methanol + water 7+2+1) afforded pure 9-(4-hydroxy-2-hydroxymethylbutyl) adenine.
^{13}C NMR (DMSO-d_6): δ 156.24 (C6); 152.67 (C2); 150.14 (C4); 141.84 (C8); 118.88 (C5); 61.18, 58.92 (2 CH_2OH); 44.81 (CH_2N); 38.36 (CH); 32.02 ($\underline{C}H_2CH_2OH$).

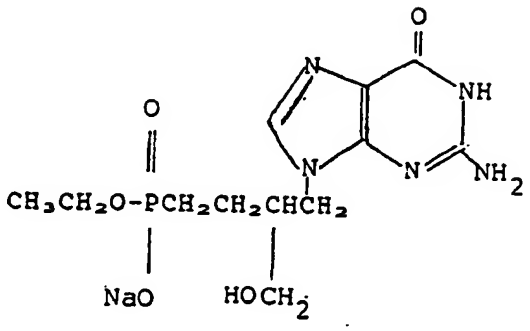
The starting material was prepared as follows:

Dimethyl 2-(adenin-9-ylmethyl)succinate

A mixture of adenine (5.40 g, 0.040 mol), dimethyl itaconate (8.00 g, 0.051 mol), sodium hydride (55 % in oil, 0.2 g) and dry N,N-dimethylformamide (125 ml) was warmed to 120°C and then kept with stirring at room temperature for 8 days. The precipitate was filtered, washed with dichloromethane (3x15 ml) and dried in vacuum to yield 8.96 g (76 %) of dimethyl 2-(adenin-9-ylmethyl)-succinate.
1H NMR ($CDCl_3$); δ 8.28 (s, 1H) H2; 7.90 (s, 1H) H8; 4.54 (ABX system 2H) CH_2N; 3.70, 3.69 (2 s, 2x3H) OCH_3; 3.46 (m, 1H) CH; 2.72 (d, 2H) CH_2COO.
13C NMR ($CDCl_3$+CD_3OD): δ 172.39, 171.42 (2 C=O); 155.61 (C6); 152.91 (C2); 149.87 (C4); 141.01 (C8); 118.85 (C5); 52.37, 51.94 (OCH3); 44.10 (CH_2N); 41.55 (CH); 33.30 ($\underline{C}H_2COO$).

Example 7 Sodium ethyl 3-(guanin-9-ylmethyl)-4-hydroxybutanephosphonate and 7 isomer

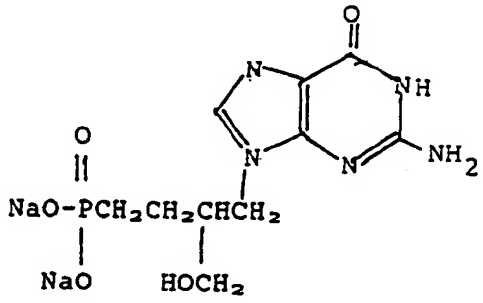
VSC 658



2-Amino-6-chloro-9-[(2-ethoxy-2-oxo-1,2-oxaphosphorinan-5-yl)-methyl]purine (VSC 655) and its 7 isomer (100 mg, 0.29 mmol), dissolved in ethanol (4 ml), water (4 ml), and 2M aqueous sodium hydroxide (0.90 mmol) was kept at 37°C for 18 h. The solution was neutralized by addition of weakly acidic Amberlite cation exchange resin, filtered, and evaporated to dryness to give 113 g (quantitative yield) of a crude product.
'H NMR (D_2O, tert BuOH, 200 Mhz); δ 8.01 and 7.79 (s, 8H, 7 and 9 isomers); ~ 4.03 (m, CH_2N); 3.78 (quintet, CH_2OP); 3.50 (d, CH_2OH); 2.05 and 1.6-1.3 (m, PCH_2CH_2CH); 1.12 (t, CH_3C-O-P).
^{13}C NMR (D_2O, tert. BuOH, 50 MHz): δ 161.81, 160.47, 154.12, 145.5, 142.13, 114.55, 61.74/61.42 (CH_2OP); 45.35 and 45.15 (CH_2N); 42.25/41.91 (CH); 25.59, 22.89; 16.83 (CH_3C-O-P).

Example 8 Disodium 3-(guanin-9-ylmethyl)-4-hydroxybutanephosphonate

VSC 660

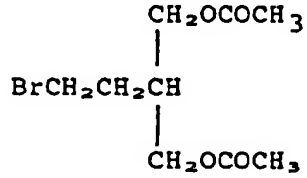


A solution of 2-amino-6-chloro-9-[(2-ethoxy-2-oxo-1,2-oxaphosphorinan -5-yl)methyl]purine (VSC 655; 102 mg, 0,295 mmol) in ethanol (2 ml), water (2 ml), and 2M aqueous sodium hydroxide (1.0 ml, 2 mmol) was kept at 80°C for 3 days, neutralized by addition of weakly acidic Amberlite cation exchange resin, filtered, and evaporated to dryness to give disodium 3-(guanin-9-ylmethyl)-4-hydroxybutanephosphonate.

The starting materials for examples 7 and 8 were prepared as follows:

2-(Acetoxymethyl)-4-bromobutyl acetate

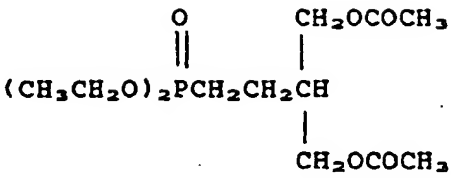
VSC 647



This intermediate was synthesized from 4-(acetoxy)-3-(acetoxymethyl)-butanol according to Literature Procedure. Yield 97% after flash chromatograpy on silica (ethyl acetate + n-hexane 1+1).
TLC R_f 0.67 (SiO_2, ethyl acetate + n-hexane 1+1).
^{13}C NMR ($CDCl_3$, TMS, 50 MHz): δ 170.30 (COO); 63.44 (CH_2O); 36.27 (CH); 31.67 (Br-CH_2); 30.29 (Br-C-CH_2); 20.51 (CH_3).

Diethyl 4-acetoxy-3-(acetoxymethyl)butanephosphonate

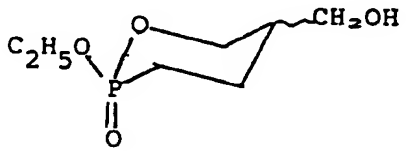
VSC 648



Triethyl phosphite (2.70g, 16.3 mmol) was added with stirring to 2-(acetoxymethyl)-4-bromobutyl acetate (VSC 647, 3.95 g, 14.8 mmol) at 180-190°C and stirring was continued at 190°C for 0.5h. The residue was evaporated in vacuum and kept at ca. 0.1 mB. Flash chromatography on silica with ethyl acetate + ethanol (9+1) yielded 3.36g (70%) of product.
TLC R_f 0.57 (SiO_2, ethyl acetate + ethanol 9+1).
^{13}C NMR ($CDCl_3$, TMS, 50 MHz): δ 170.37 (COO); 63.22 (CH_2OAc); 61.30/61.18 (CH_2OP, J 6 Hz); 37.58/37.27 (CH, J 16 Hz); 24.11/21.29 (CH_2-C-P, J 142 Hz); 20.97/20.90 (CH_2P J 4 Hz); 20.46 (CH_3COO); 16.20/16.08, J 6 Hz.

(2-Ethoxy-2-oxo-1,2-oxaphosphorinan-5-yl)methanol (racemic cis-trans mixture)

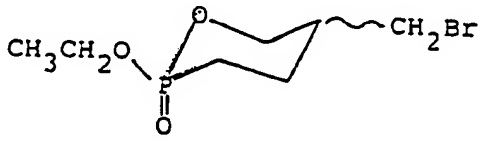
VSC 650



VSC 648 (1.05; 3.24 mmol) was dissolved in 16 ml of a 0.5 molar solution of sodium ethoxide in ethanol. The solution was warmed to 50°C and then kept at 37°C for 2 h. After evaporation to dryness in vacuum, the residue was extracted with ethyl acetate and purified by flash chromatography on silica with ethyl acetate + ethanol (9+1) as eluent. Yield 0.462 g (74%) of VSC 650 in an isomeric (cis-trans) ratio of 0.36/1.00.
TLC R_f 0.26 (SiO_2; ethyl acetate + ethanol 9+1).
^{13}C NMR ($CDCl_3$, TMS, 50 MHz); major isomer - minor isomer): δ 72.22/72.08 - 70.64/70.52 (CH_2O in ring, J 6 Hz); 62.18 - 63.64 (CH_2OH); 60.81/60.69 - 61.35/61.23 (CH_2-O-P, J 6 Hz); 38.87/38.75 - 37.39/37.27 (CH, J 6 Hz); 24.69/24.52 - 23.35/23.18 (CH_2-P, J 8 Hz); 23.06/20.48 - 21.38/18.80 (CH_2-C-P, J 129 Hz); 16.25/16.15 (CH_3-C-O-P, J 5 Hz).

5-(Bromoethyl)-2-ethoxy-2-oxo-1,2-oxaphosphorinane (racemic cis-trans mixture

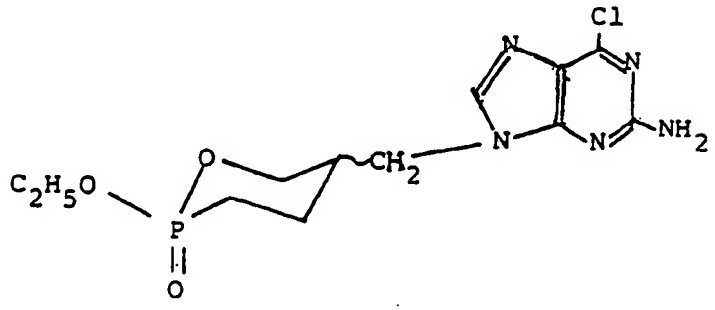
VCS 654



N-Bromosuccinimide (2.67g, 15 mmol) was added in portions to a stirred, ice-chilled solution of 2-ethoxy-2-oxo-1,2-oxaphosphorinan-5-yl)methanol (VSC 650, 1.944 g, 10 mmol) and triphenylphosphine (3.97 g, 15 mmol) in 40 ml of dichloromethane, and stirring was continued for 16h at 4°C. After evaporation in vacuum, diethyl ether (50 ml) was added and the mixture shaken and stirred vigorously. The crystallized triphenylphosphine oxide was removed by filtration and washed with several portions of ether. The combined extracts were evaporated to dryness and purified by flash chromatography on silica with ethyl acetate + ethanol (9+1). Yield 1.569 g (61%) of VSC 654 in a cis-trans ratio of 0.7/1.0. TLC Rf 0.57 (SiO_2 ethyl acetate + ethanol 9+1).
^{13}C NMR ($CDCl_3$, TMS, 50 MHz, major isomer - minor isomer): δ 71.76/71.61 (CH_2O in ring, J 6 Hz); 60.74/60.62-61.20/61.08 (CH_2-O-P, J 16 Hz); 37.56/37.44-37.10/36.98 (CH, J 6 Hz); 32.13-31.67 (CH_2Br); 26.66/26.49-25.37/25.23 (CH_2P, J 7 Hz) 22.60/20.02-20.90/18.32 (CH_2-C-P, J 129.4 Hz); 16.13/16.01 (CH_3-C-O-P, J 6.1 Hz).

2-Amino-6-chloro-9-[(2-ethoxy-2-oxo-1,2-oxaphosphorinan-5-yl)methyl] purine and 7 isomer

VSC 655



A mixture of 5-(bromoethyl)-2-ethoxy-2-oxo-1,2-oxaphosphorinane (VSC 654; 0.353 g, 1.82 mmol), 2-amino-6-chloropurine (0.50, 2.95 mmol), anhydrous potassium carbonate (0.50 g, 3.62 mmol), and DMF (15 ml) was stirred at room temperature for seven days. Chloroform (30 ml) was added, and after filtration, the solution was evaporated to small volume in vacuum. The residue was purified by flash chromatography on silica (chloroform + methanol 5+1). Yield 0.282 g (45%) as a cis-trans and 7-9 isomeric mixture.
TLC $_{Rf}$ 0.74 and 0.68 for 7 and 9 isomer, respectively (SiO_2, chloroform + methanol 5+1).
1H NMR ($CDCl_3$, TMS, 200 MHz): δ 7.80 and 7.76 (s, H8, 7 and 9 isomer); 5.4 (broad s, NH_2); 4.3-4.1 (m, CH_2OP); 4.02 (d, CH_2N); 2.5-2.4 and 2.1-1.7 (m, $CHCH_2CH_2P$); 1.37 (dt, CH_3- COP).
^{13}C NMR ($CDCl_3$, TMS, 50 MHz): δ 159.38 (C_2); 153.93 (C4); 143.50 (C8); 70.91/70.79-69.94/69.79 (CH_2O in ring, J 7 Hz) 61.79 to 61.45 (2 d, CH_2-O-P, J 7 Hz); 44.35 and 43.25 (CH_2N); 36.68/36.56-35.05/34.93 (CH, J, 6 Hz); 25.88/25.74-24.18/24.04 (CH_2P, J 7 Hz); 22.99/20.41-21.16/18.59 (CH_2-C-P, J 129 Hz); 16.59/16.47 (CH_3-C-O-P, J 6 Hz).

Biological tests

Test I Effect of compounds of the formula I on HIV in H9 cells

Materials and methods: HIV infection of H9 cells

H9 cells, 10^5 cells per well on a 24 well plate, suspended in 2 ml RPMI-medium containing 10 % fetal calf serum, 100 µg/ml pencillin, 10 µg/ml streptomycin sulfate and 2 µg/ml polybrene are exposed to HIV (HTLV-IIIB) and different concentrations of the test compounds. The plates are incubated at 37°C in 5 % CO_2 for 6-7 days. The contents in each well is then homogenized with a pipette and transferred to a centrifuge tube. After centrifugation for 10 min at 1500 rpm the supernatant is removed and the cell pellet is analyzed by fixing in methanol on glass plates. Human HIV positive serum diluted 1:80 or 1:160 is added and incubated for 30 min at 37°C. The plate is then washed with phosphate-buffered saline (PBS) containing Ca2+ and Mg2+. Sheep antihuman conjugate (FITC) is added and after a new incubation the plate is again washed with PBS. Contrast staining is done with Evans blue and after drying the frequency of HIV antigen containing cells is determined in a microscope. The test result is shown in Table I.

Table I Concentration (μM) for 50 % inhibition (IC_{50}) of human immuno deficiency virus multiplication in cell culture

Compounds	IC_{50} M
9-[4-hydroxy-2-(hydroxymethyl)butyl]-guanine (VSA 671)	1-10
(-)-9-[4-hydroxy-2-(hydroxymethyl)butyl]-guanine (VSB 647)	0.1-7
(+)-9-[4-hydroxy-2(hydroxymethyl)butyl]-guanine (VSB 648)	1-5
9-[4-hydroxy-2-(hydroxymethyl)butyl]-adenine (VSL 600)	10

Table I shows that the tested compounds are active inhibitors of HIV virus multiplication.

Test II Cellular toxicity

H9 cells, $2x10^7$ cells per plate, are incubated in RPMI-1640 medium containing 10 % fetal calf serum, 70 mg/l penicillin, 100 mg/l streptomycin and 10 mM hepes, in absence or presence of test compounds. The number of cells per plate is determined after 48 h. Cells incubated in the absence of test compounds then underwent two cell division cycles.

F5000 cells, which are human embryo cells, $1x10^5$ cells per plate, are incubated in Eagle's minimal essential medium, supplemented with Earle's salts, non-essential amino acids, 10 % fetal calf serum, 10 mM hepes, 70 mg/l penicillin and 10 mg/l streptomycin, in absence or presence of test compounds. The number of cells per plate is determined after 48 h. Cells incubated in the absence of test compounds underwent one cell division cycle. The results are given as % inhibition of cell multiplication when the concentration of the compounds is 100 μM or 250 μM.

Table II Cellular toxicity on H9 and F5000 cells

Compound	% inhibition (concentration μM) H9	F5000
9-[4-hydroxy-2-(hydroxymethyl)-butyl]guanine (VSA 671)	55 (500)	55(1000)
(-)-9-[4-hydroxy-2-(hydroxymethyl)-butyl]guanine (VSB 647)	5 (100)	
9-[4-hydroxy-2-(hydroxymethyl) butyl]-adenine (VSc 600)	25 (200)	25 (500)
2-(2-aminopurin-9-yl)methyl-butan-1,4-diol (VSB 212)		20 (500)
		75 (500)

Table II shows that the concentrations at which the compounds exhibit toxicities, vastly exceed the concentrations needed for 50 % inhibition of HIV multiplications as given in Table I.

Test III Oral bioavailability

Oral bioavailability was determined by dosing the animals (cynomologous monkeys and rats) intravenously and orally on separate occasions with the compounds. Blood samples were taken after appropriate intervals for determination of drug level in plasma. Appropriate pharmacokinetic calculations were then carried out based on plasma concentration against time relationship.

Table III Oral bioavailability of compound determined as VSA 671

Compound	F* %
Monkey	
9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (VSA 671)	10
2-(2-aminopurin-9-yl)methylbutane-1,4-diol diacetate (VSC 610)	32
Rat	
9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (VSA 671)	11
9-[4-acetoxy-2-(acetoxymethyl)butyl]guanine.HCl (VSC 640)	20
9-[4-propionoxy-2-(propionoxymethyl)butyl]guanine.HCl (VSC 641)	19
2-(2-aminopurin-9-yl)methylbutan-1,4-diol (VSB 212)	26

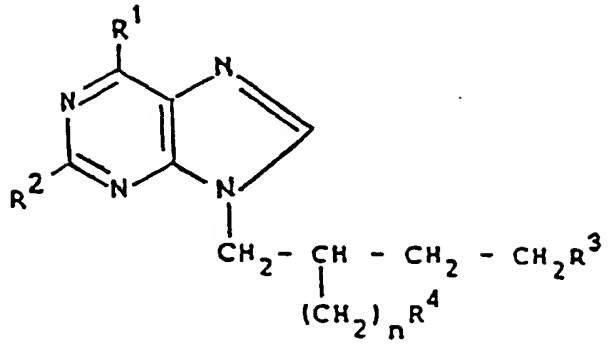
*Plasma AUC (area under curve) of compound relative to AUC after intravenously given VSA 671.

From the table can be seen how the plasma concentration of VSA 671 is significantly increased after VSA 671 has been given as a 6-deoxy prodrug (VSB 212), and ester (VSC 640, VSC 641) or an ester of 6-deoxy prodrug (VSC 610).

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula



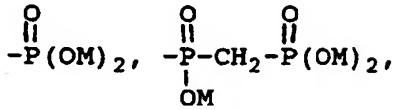
I

wherein:

R^1 is hydrogen, hydroxy, mercapto or amino;

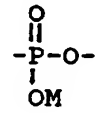
R^2 is hydrogen, hydroxy, fluoro, chloro or amino;

R^3 and R^4 are independently selected from



amino, hydroxy

or an ester residue thereof defined as OR^5, wherein R^5 is C_{1-6} alkyl, arylalkyl, optionally substituted with one or more alkoxy, amino, nitrile or sulphonamido groups or one or more halogen atoms or an ester residue thereof derived from a carboxylic acid R^6COOH, a carbonic acid R^7OCOOH, a double ester of a carbonic acid R^7CO-$OCH(R^8)OCOOH$, a sulphonic acid R^7SO_2OH, a carbamic acid $R^7NHCOOH$, or a phosphoric acid, wherein R^6 is hydrogen, C_{1-17} alkyl, alkoxyalkyl, arylalkyl or aryl, R^7 is C_{1-17} alkyl, arylalkyl or aryl, R^8 is hydrogen or C_{1-13} alkyl and said aryl and arylalkyl groups optionally can be substituted with one or more alkyl, alkoxy, amino, nitrile, sulphonamido groups or one or more halogen atoms ,or R^3 together with R^4 is



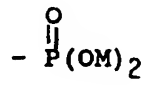
wherein

M is hydrogen or a pharmaceutically acceptable counterion; and n is 1 or 2; with the proviso that, when R^2 is amino and R^3 and R^4 are hydroxy, R^1 is not hydroxy and in addition, when n = 1, R^1 is not hydrogen, and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 in the form of an optical isomer.

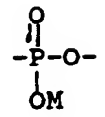
3. A compound according to claim 1 or 2, wherein R^3 and R^4 are both hydroxy.

4. A compound according to claim 1 or 2, wherein R^3 is



and R^4 is OH or

R^3 together with R^4 is



5. A compound according to any of claims 1-4 for use in therapy.

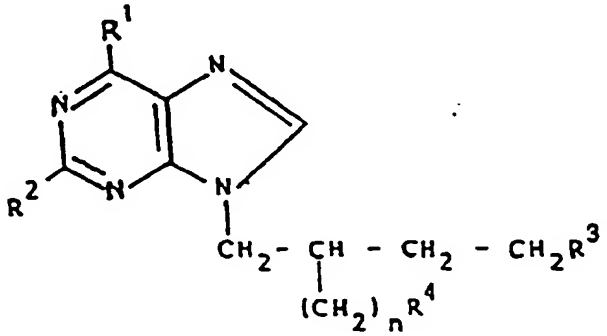
6. A compound of the formula I as defined in any of claims 1-4 for therapeutic and/or prophylactic treatment of virus infections in an animal or human host in the need of treatment.

7. A compound according to claim 6 for treatment of infections caused by herpes viruses.

8. A compound according to claim 6 for treatment of infections caused by viruses requiring reverse transcriptase for replication, including human immuno deficiency viruses and hepatitis B virus.

9. A pharmaceutical composition comprising as active ingredient a compound according to any of claims 1-4 and a pharmaceutically acceptable carrier.

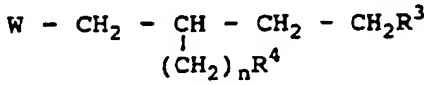
10. A process for preparation of a compound of the formula



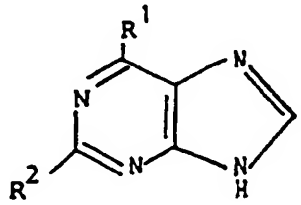
I

wherein R^1, R^2, R^3, R^4 and n are as defined in claim 1, by

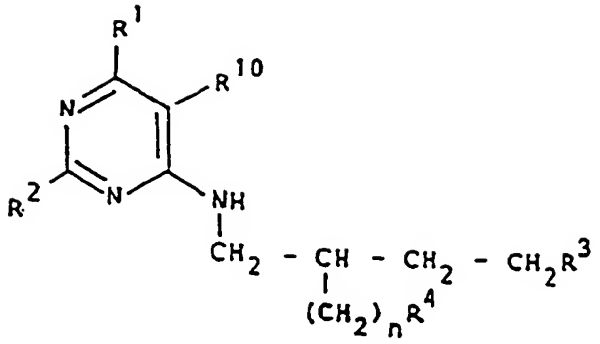
A. condensing an acyclic side chain



where W is a terminal leaving group, to the N-9 position of a purine derivative

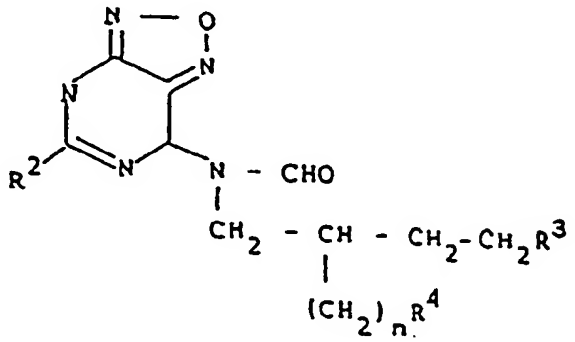


B. imidazole ring closure of a pyrimidine derivative thereof of the formula



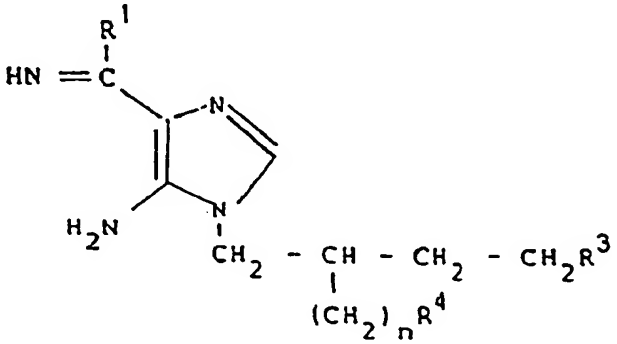
wherein R is amino or an amino derivative;

C. imidazole ring closure of a furazano-[3,4-d]pyrimidine ring of the formula



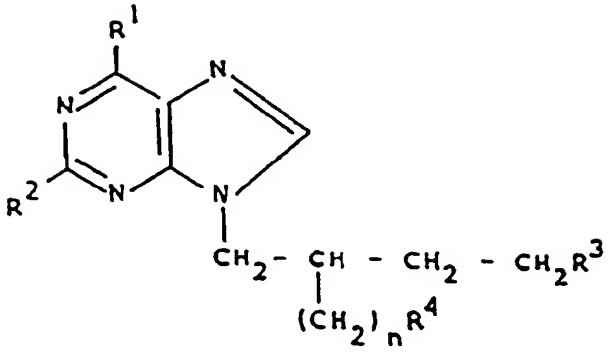
and reductive cleavage of the furazane ring to a compound of the formula I, wherein R^1 is amino; or

D. pyrimidine ring closure of an imidazole derivative of the formula



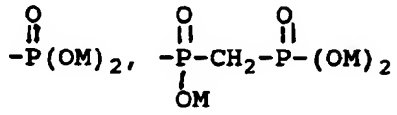
in which processes R^1 - R^4 and n are as defined in claim 1 and optionally may be protected by suitable protecting groups, whereby a mixture of optical isomers or a single optical isomer is obtained and a racemic mixture obtained is optionally separated into the optical isomers.

11. Use of a compound of the formula I

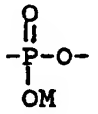


I

wherein:
R^1 is hydrogen, hydroxy, mercapto or amino;
R^2 is hydrogen, hydroxy, fluoro, chloro or amino;
R^3 and R^4 are independently selected from



amino, hydroxy
or an ether residue thereof defined as OR_5, wherein R^5 is C_{1-6} alkyl, arylalkyl optionally substituted with one or more alkoxy, amino, nitrile, or sulphonamido groups or one or more halogen atoms,
or an ester residue thereof derived from a carboxylic acid R^6COOH, a carbonic acid R^7OCOOH, a double ester of a carbonic acid $R^7COOCH(R^8)OCOOH$, a sulphonic acid R^7SO_2OH, a carbamic acid $R^7NHCOOH$, or a phosphoric acid, wherein R^6 is hydrogen, C_{1-17} alkyl, alkoxyalkyl, arylalkyl or aryl, R^7 is C_{1-17} alkyl, arylalkyl or aryl, R^8 is hydrogen or C_{1-3} alkyl and said aryl and arylalkyl groups optionally can be substituted with one or more alkyl, alkoxy, amino, nitrile, sulphonamido groups or one or more halogen atoms or R^3 together with R4 is



wherein
M is hydrogen or a pharmaceutically acceptable counterion; and n is 1 or 2; and pharmaceutically acceptable salts thereof for the manufacture of a medicament for therapeutic and/or prophylactic treatment of the acquired immuno deficiency syndrome and infections caused by viruses requiring reverse transcriptase for replication.

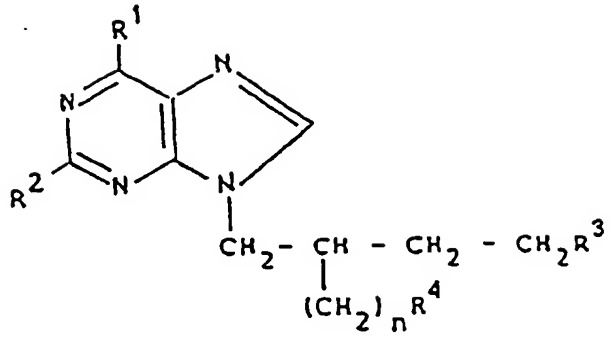
12. Use of a compound of the formula according to claim 11 in the form of an optical isomer.

13. Use according to claim 11 or 12 for the treatment of infections caused by HIV-viruses.

14. Use according to claim 11 or 12 for the treatment of infections caused by hepatitis B viruses.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of a compound of the formula



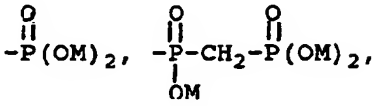
I

wherein:

R^1 is hydrogen, hydroxy, mercapto or amino;

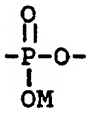
R^2 is hydrogen, hydroxy, fluoro, chloro, or amino;

R^3 and R^4 are independently selected from



amino, hydroxy

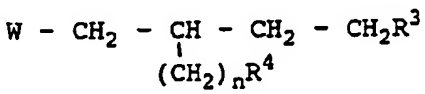
or an ether residue thereof defined as OR^5, wherein R^5 is C_{1-6} alkyl, arylalkyl optionally substituted with one or more alkoxy amino, nitrile or sulphonamido group or one or more halogen atoms or an ester residue thereof derived from a carboxylic acid R^6COOH, a carbonic acid R^7OCOOH, a double ester of a carbonic acid $R^7CO-OCH(R^8)OCOOH$, a sulphonic acid R^7SO_2OH, a carbamic acid $R^7NHCOOH$, or a phosphoric acid, wherein R^6 is hydrogen, C_{1-17} alkyl, alkoxyalkyl, arylalkyl or aryl, R^7 is C_{1-17} alkyl, arylalkyl or aryl, R^8 is hydrogen or C_{1-13} alkyl and said aryl and arylalkyl groups optionally can be substituted with one or more alkyl, alkoxy, amino, nitrile, sulphonamido groups or one or more halogen atoms, or R^3 together with R^4 is



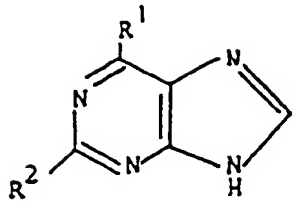
wherein

M is hydrogen or a pharmaceutically acceptable counterion; and n is 1 or 2; with the proviso that, when R^2 is amino and R^3 and R^4 are hydroxy, R^1 is not hydroxy and in addition, when n = 1, R^1 is not hydrogen, and pharmaceutically acceptable salts thereof, by

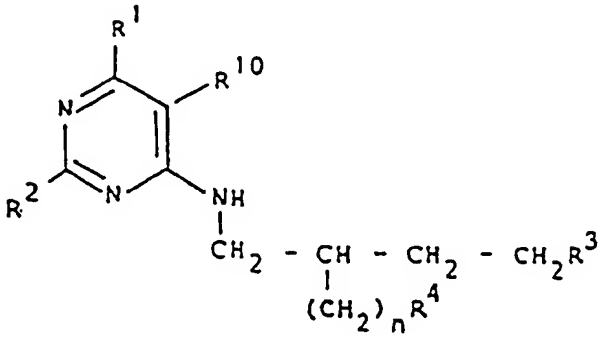
A. condensing an acyclic side chain



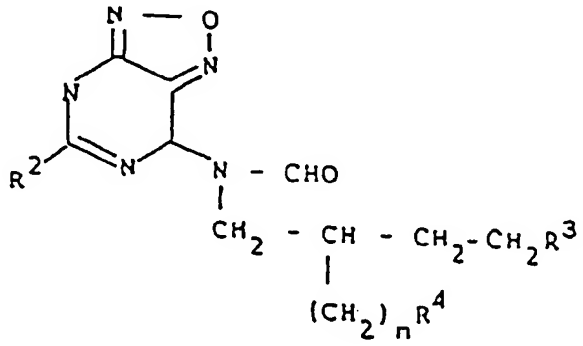
where W is a terminal leaving group, to the N-9 position of a purine derivative



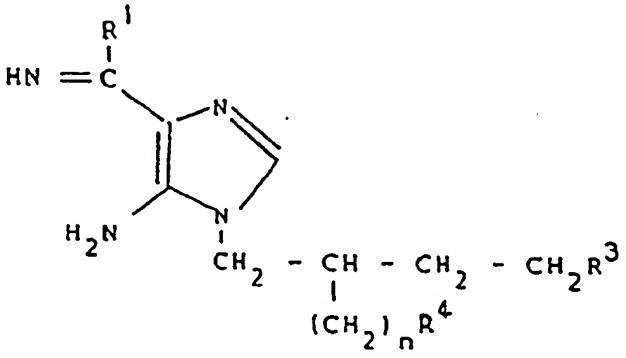
B. imidazole ring closure of a pyrimidine derivative thereof of the formula



wherein R is amino or an amino derivative;
C. imidazole ring closure of a furazano-[3,4-d]pyrimidine ring of the formula



and reductive cleavage of the furazane ring to a compound of the formula I, wherein R^1 is amino; or
D. pyrimidine ring closure of an imidazole derivative of the formula



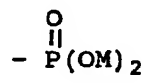
in which processes R^1 - R^4 and n are as defined above and optionally may be protected by suitable protecting groups, whereby a mixture of optical isomers or a single optical isomer is obtained and a racemic mixture obtained is optionally separated into the optical isomers.

2. A process according to claim 1 for preparation of a compound of the formula I in the form of an optical isomer.

3. A process according to claim 1 or 2 for preparation of a compound of the formula I, wherein R^3 and R^4 are both hydroxy.

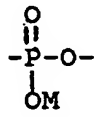
4. A process according to claim 1 or 2 for the preparation of a compound of the formula I wherein

R^3 is



and R^4 is OH or

R^3 together with R^4 is



5. A process for preparing a compound according to any of claims 1-4 for use in therapy.

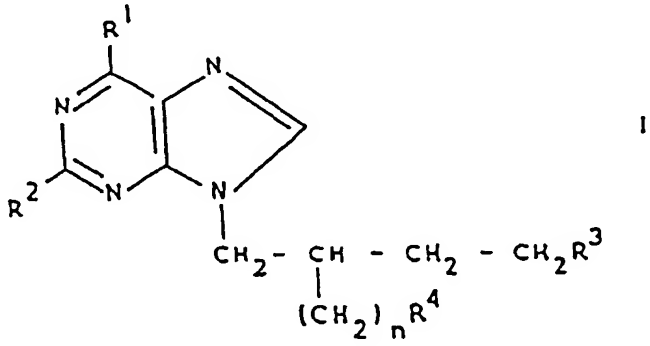
6. A process for preparing a compound of the formula I as defined in any of claims 1-4 for therapeutic and/or prophylactic treatment of virus infections in an animal or human host in the need of treatment.

7. A process for preparing a compound according to claim 6 for treatment of infections caused by herpes viruses.

8. A process for preparing a compound according to claim 6 for treatment of infections caused by viruses requiring reverse transcriptase for replication, including human immuno deficiency viruses and hepatitis B virus.

9. A process for preparing a pharmaceutical composition comprising combining, as active ingredient, a compound according to any of claims 1-4 with a pharmaceutically acceptable carrier.

10. Use of a compound of the formula I



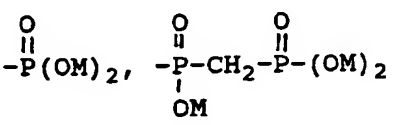
I

wherein:

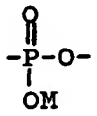
R^1 is hydrogen, hydroxy, mercapto or amino;

R^2 is hydrogen, hydroxy, fluoro, chloro or amino;

R^3 and R^4 are independently selected from



amino, hydroxy
or an ether residue thereof defined as OR_5, wherein R^5 is C_{1-6} alkyl, arylalkyl optionally substituted with one or more alkoxy, amino, nitrile or sulphonamido groups or one or more halogen atoms,
or an ester residue thereof derived from a carboxylic acid R^6COOH, a carbonic acid R^7OCOOH, a double ester of a carbonic acid $R^7COOCH(R^8)OCOOH$, a sulphonic acid R^7SO_2OH, a carbamic acid $R^7NHCOOH$, or a phosphoric acid, wherein R^8 is hydrogen, C_{1-17} alkyl, alkoxyalkyl, arylalkyl or aryl, R^7 is C_{1-17} alkyl, arylalkyl or aryl, R^8 is hydrogen or C_{1-3} alkyl and said aryl and arylalkyl groups optionally can be substituted with one or more alkyl, alkoxy, amino, nitrile, sulphonamido groups or one or more halogen atoms or R^3 together with R4 is



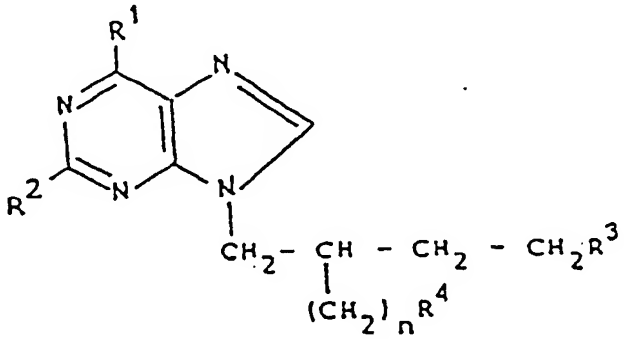
wherein
M is hydrogen or a pharmaceutically acceptable counterion; and n is 1 or 2; and pharmaceutically acceptable salts thereof for the manufacture of a medicament for therapeutic and/or prophylactic treatment of the acquired immuno deficiency syndrome and infections caused by viruses requiring reverse transcriptase for replication.

11. Use of a compound of the formula according to claim 10 in the form of an optical isomer.
12. Use according to claim 10 or 11 for the treatment of infections caused by HIV-viruses.
13. Use according to claim 10 or 11 for the treatment of infections caused by hepatitis B viruses.

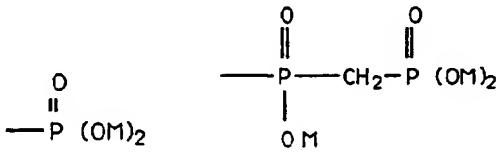
Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel I

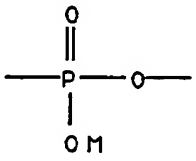


worin sind:
R^1 ein Wasserstoffatom, eine Hydroxy-, Mercapto- oder Aminogruppe;
R^2 ein Wasserstoffatom, eine Hydroxygruppe, ein Fluoratom, ein Chloratom oder eine Aminogruppe;
R^3 und R^4 voneinander unabhängig ausgewählt aus



Amino-, Hydroxy- oder einem Etherrest,
definiert als OR^5, worin R^5 ein C_{1-6}-Alkyl, ein Arylalkyl - wahlweise substituiert mit ein oder mehreren Alkoxy-, Amino-, Nitril- oder Sulphonamidgruppen oder mit ein oder mehreren Halogenatomen oder einem Esterrest

davon, der ableitbar ist aus einer Carbonsäure R^6COOH, einer Kohlensäureesterverbindung R^7OCOOH, einem Doppelester der Kohlensäure $R^7COOCH(R^8)OCOOH$, einer Sulphonsäure R^7SO_2OH, einer Carbaminsäure $R^7NHCOOH$, einer Phosphorsäure, worin,sind: R^6 gleich Wasserstoff, C_{1-17}-Alkyl, Alkoxyalkyl, Arylalkyl oder Aryl; R^7 ein C_{1-17}-Alkyl, Arylalkyl oder Aryl, R^8 ein Wasserstoffatom oder ein C_{1-13}-Alkyl, wobei die Aryl- und Arylalkylgruppen wahlweise mit ein oder mehreren Alkyl-, Alkoxy-, Amino-, Nitril-, Sulphonamidgruppen oder ein oder mehreren Halogenatomen substituiert sein können, oder R^3 zusammen mit R^4 ein

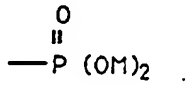


sind, worin
M ein Wasserstoffatom oder ein pharmazeutisch verwendbares Gegenion ist;
und n = 1 oder 2; unter den Voraussetzungen: wenn R^2 eine Aminogruppe und R^3 und R^4 Hydroxygruppen sind, daß dann R^1 keine Hydroxygruppe ist und zusätzlich, wenn n gleich 1 ist, daß R^1 kein Wasserstoffatom ist; sowie pharmazeutisch akzeptable Salze davon.

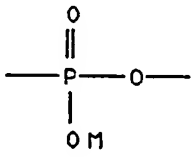
2. Verbindung gemäß Anspruch 1 in der Form eines optischen Isomers.

3. Verbindung gemäß Anspruch 1 oder 2, worin R^3 und R^4 beide Hydroxygruppen sind.

4. Verbindung gemäß Anspruch 1 oder 2, worin sind:
R^3 gleich



und R^4 ein OH oder
R^3 zusammen mit R^4 ein



5. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 4 in der Therapie.

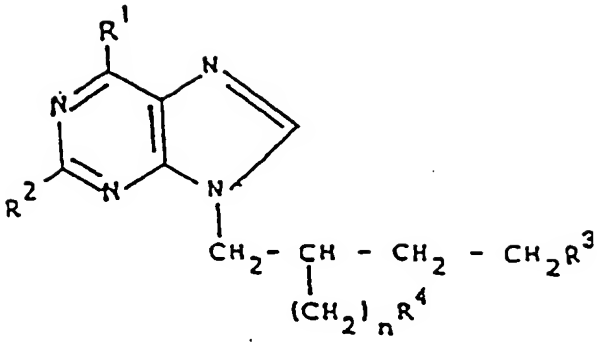
6. Verbindung der Formel I gemäß einem der Ansprüche 1 bis 4 zur therapeutischen und/oder prophylaktischen Behendlung von Virusinfektionen bei behandlungsbedürftigen Tieren oder Menschen.

7. Verbindung gemäß Anspruch 6 zur Behandlung von Infektionen aufgrund von Herpes-Viren.

8. Verbindung gemäß Anspruch 6 zur Behandlung von Infektionen weger Viren, die zur Replikation reverse Transkriptase benötigen, einschließlich des menschlichen Immunschwäche-viruses und des Hepatits-B-Viruses.

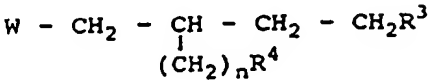
9. Pharmazeutische Zusammensetzung, die als Wirksubstanz eine Verbindung gemäß einem der Ansprüche 1 bis 4 enthält sowie einen pharmazeutisch akzeptablen Träger.

10. Verfahren zur Herstellung einer Verbindung der Formel I

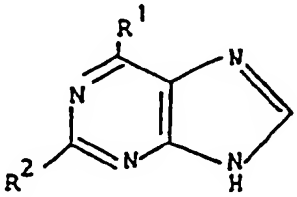


worin sind R^1, R^2, R^3, R^4 und n wie in Anspruch 1 definiert, durch

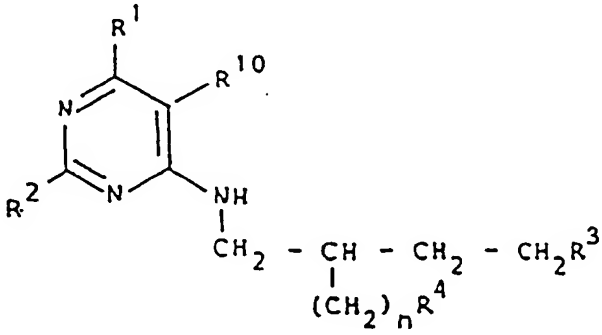
A. Kondensation einer acylischen Seitenkette



worin W eine terminale Abgangsgruppe ist, an die N-9-Position des Purinderivates

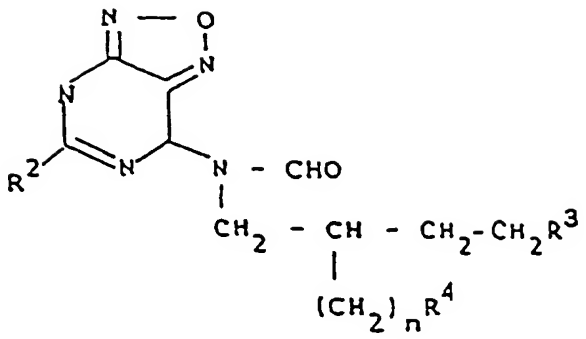


B. Imidazol-Ringschluß des Pyrimidinderivats der Formel



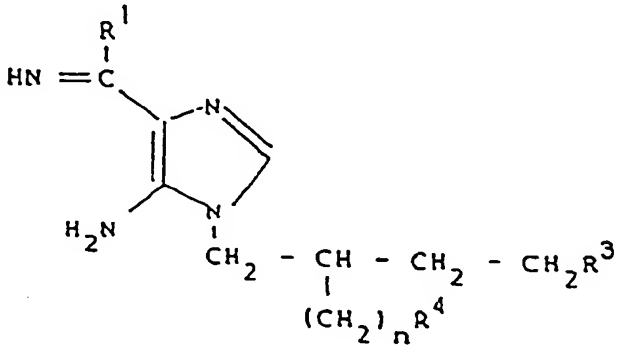
worin R eine Aminogruppe ist oder ein Aminoderivat;

C. Imidazol-Ringschluß des Furazano-[3,4-d]pyrimidin-Rings der Formel



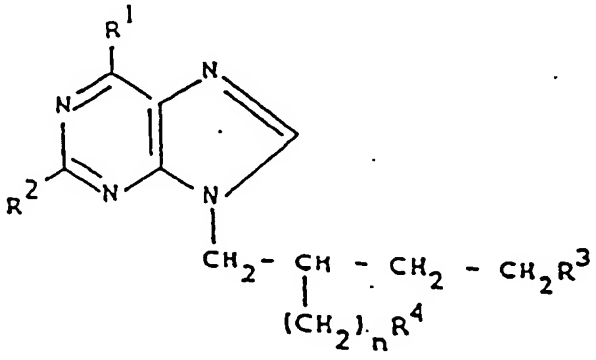
und Reduktionsspaltung des Furazanringes der Verbindung der Formel I, worin R^1 eine Aminogruppe ist; oder

D. Pyrimidin-Ringschluß eines Imidazol-Derivates der Formel



worin die Fortsätze R^1 bis R^4 und n wie in Anspruch 1 definiert und wahlweise durch geeignete Schutzgruppen geschützt sind, wobei eine Mischung der optischen Isomere oder ein einziges optisches Isomer erhalten wird und racemische Mischungen wahlweise in die optischen Isomere aufgetrennt werden.

11. Verwendung einer Verbindung der Formel I

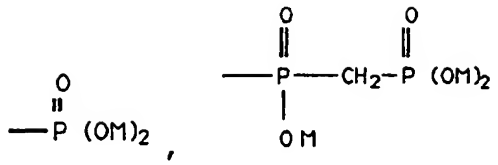


worin sind:

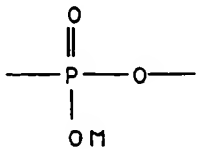
R^1 ein Wasserstoffatom, eine Hydroxy-, Mercapto- oder Aminogruppe;

R^2 ein Wasserstoffatom, eine Hydroxygruppe, ein Fluor-, Chloratom oder eine Aminogruppe;

R^3 und R^4 unabhängig voneinander ausgewählt aus



Amino-, Hydroxy- oder einem Etherrest, der definiert ist als OR^5, worin R^5 ein C_{1-6}-Alkyl, ein Arylalkyl, das wahlweise mit ein oder mehreren Alkoxy-, Amino-, Nitril- oder Sulphonamidgruppen oder ein oder mehreren Halogenatomen substituiert sind oder einem Esterrest, der abgeleitet ist aus der Carbonsäure R^6COOH, dem Kohlensäureester R^7OCOOH, dem zweifachen Kohlensäureester $R^7COOCH(R^8)OCOOH$, der Sulphonsäure R^7SO_2OH, der Carbaminsäure $R^7NHCOOH$ oder eine Phosphorsäure, worin sind: R^6 ein Wasserstoffatom, C_{1-17}-Alkyl, ein Alkoxyalkyl, ein Arylalkyl oder Aryl ist, wobei R^1 ein C_{1-17}-Alkyl, Arylalkyl oder Aryl ist, R^8 ein Wasserstoffatom oder ein C_{1-3}-Alkyl ist und die besagten Aryl- und Arylalkylgruppen substituiert sein können mit ein oder mehreren Alkyl-, Alkoxy-, Amino-, Nitril-, Sulphonamid-gruppen oder ein oder mehreren Halogenatomen oder R^3 zusammen mit R^4 ein



worin M ein Wasserstoffatom oder ein pharmazeutisch akzeptables Gegenion ist; und n gleich 1 oder 2 ist; und pharmazeutisch akzeptable Salze davon, zur Herstellung eines Medikaments zur therapeutischen und/oder prophylaktischen Behandlung des erworbenen Immunschwäche-Syndroms und von Infektionen aufgrund von Viren, die zur Replikation reverse Transkriptase benötigen.

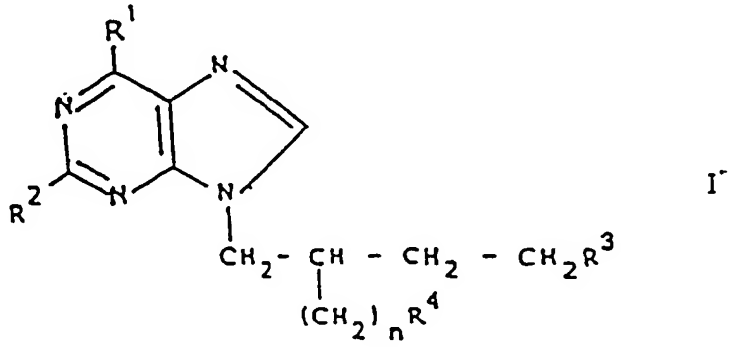
12. Verwendung einer Verbindung der Formel gemäß Anspruch 11 in Form eines optischen Isomers.

13. Verwendung gemäß Anspruch 11 oder 12 zur Behandlung von Infektionen aufgrund von HIV-Viren.

14. Verwendung gemäß Anspruch 11 oder 12 zur Behandlung von Infektionen aufgrund von Hepatis-B-Viren.

Patentansprüche für folgende Vertragstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel I

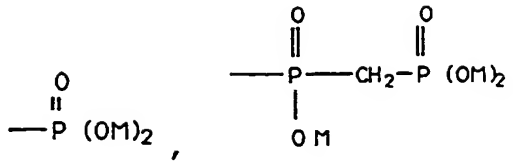


worin sind:

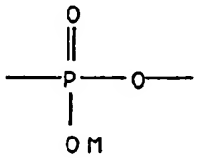
R^1 ein Wasserstoffatom, eine Hydroxy-, Mercapto- oder Aminogruppe;

R^2 ein Wasserstoffatom, eine Hydroxygruppe, ein Fluoratom, ein Chloratom oder eine Aminogruppe;

R^3 und R^4 voneinander unabhängig ausgewählt aus

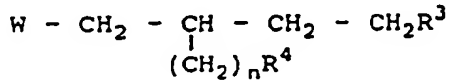


Amino-, Hydroxy- oder einem Etherrest,
definiert als OR^5, worin R^5 ein C_{1-6}-Alkyl, ein Arylalkyl - wahlweise substituiert mit ein oder mehreren Alkoxy-, Amino-, Nitril- oder Sulphonamidgruppen oder mit ein oder mehreren Halogenatomen oder einem Esterrest davon, der ableitbar ist aus einer Carbonsäure R^6COOH, einer Kohlensäureesterverbindung R^7OCOOH, einem Doppelester der Kohlensäure $R^7COOCH(R^8)OCOOH$, einer Sulphonsäure R^7SO_2OH, einer Carbaminsäure $R^7NHCOOH$, einer Phosphorsäure, worin,sind: R^6 gleich Wasserstoff, C_{1-17}-Alkyl, Alkoxyalkyl, Arylalkyl oder Aryl; R^7 ein C_{1-17}-Alkyl, Arylalkyl oder Aryl, R^8 ein Wasserstoffatom oder ein C_{1-13}-Alkyl, wobei die Aryl- und Arylalkylgruppen wahlweise mit ein oder mehreren Alkyl-, Alkoxy-, Amino-, Nitril-, Sulphonamidgruppen oder ein oder mehreren Halogenatomen substituiert sein können, oder R^3 zusammen mit R^4 ein

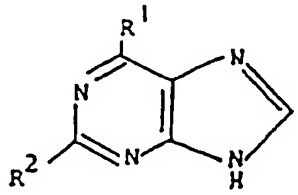


sind, worin
M ein Wasserstoffatom oder ein pharmazeutisch verwendbares Gegenion ist; und n = 1 oder 2; unter den Voraussetzungen: wenn R^2 eine Aminogruppe und R^3 und R^4 Hydroxygruppen sind, daß dann R^1 keine Hydroxygruppe ist und zusätzlich, wenn n gleich 1 ist, daß R^1 kein Wasserstoffatom ist; sowie pharmazeutisch akzeptable Salze davon. durch

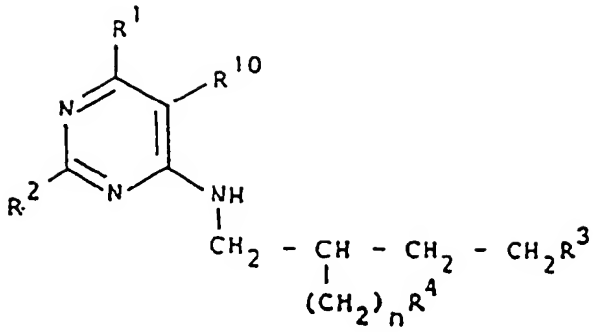
A. Kondensation einer acylischen Seitenkette



worin W eine terminale Abgangsgruppe ist, an die N-9-Position des Purinderivates

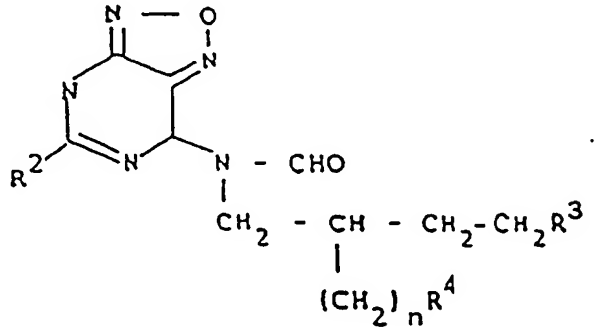


B. Imidazol-Ringschluß des Pyrimidinderivats der Formel



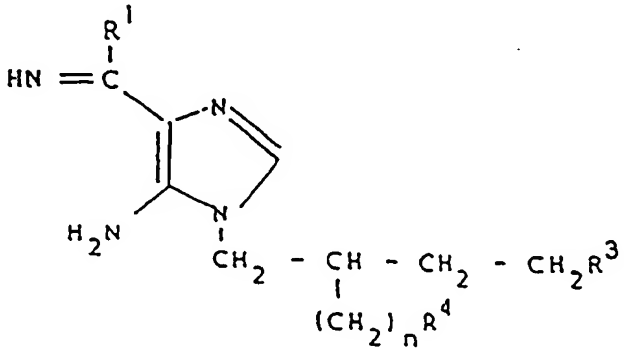
worin R eine Aminogruppe ist oder ein Aminoderivat;

C. Imidazol-Ringschluß des Furazano-[3,4-d]pyrimidin-Rings der Formel



und Reduktionsspaltung des Furazanringes der Verbindung der Formel I, worin R^1 eine Aminogruppe ist; oder

D. Pyrimidin-Ringschluß eines Imidazol-Derivates der Formel

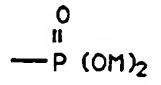


worin die Fortsätze R^1 bis R^4 und n wie in Anspruch 1 definiert und wahlweise durch geeignete Schutzgruppen geschützt sind, wobei eine Mischung der optischen Isomere oder ein einziges optisches Isomer erhalten wird und racemische Mischungen wahlweise in die optischen Isomere aufgetrennt werden.

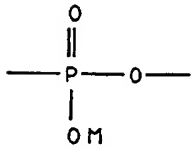
2. Verfahren gemäss Anspruch 1 zur Herstellung einer Verbindung der Formel I in der Form eines optischen Isomes.

3. Verfahren gemäss Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel I, worin R^3 und R^4 beide Hydroxygruppen sind.

4. Verbindung gemäss Anspruch 1 oder 2, zur Herstellung einer Verbindung der Formel I, worin sind: R^3 gleich



und R^4 ein OH oder
R^3 zusammen mit R^4 ein



5. Verfahren zur Herstellung einer Verbindung gemäss einem der Ansprüche 1 bis 4 in der Therapie.

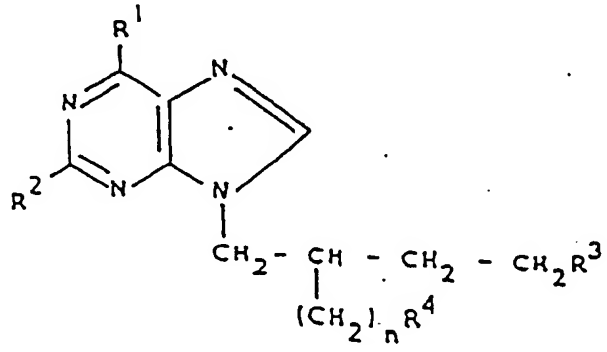
6. Verfahren zur Herstellung einer Verbindung der Formel I gemäss einem der Ansprüche 1 bis 4 zur therapeutischen und/oder prophylaktischen Behandlung von Virusinfektionen bei behandlungsbedürftigen Tieren oder Menschen.

7. Verfahren zur Herstellung einer Verbindung gemäss Anspruch 6 zur Behandlung von Infektionen aufgrund von Herpes-Viren.

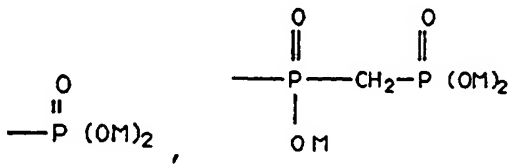
8. Vervahren zur Herstellung einer Verbindung gemäss Anspruch 6 zur Behandlung von Infektionen wegen Viren, die zur Replikation reverse Transkriptase benötigen, einschliesslich des menschlichen Immunschwächeviruses und des Hepatits-B-Viruses.

9. Verfahren zur Herstellung einer pharmazeutische Zusammensetzung durch Kombination einer Verbindung gemäss einem der Ansprüche 1 bis 4 als Wirksubstanz und eines pharmazeutisch akzeptablen Träger.

10. Verwendung einer Verbindung der Formel I

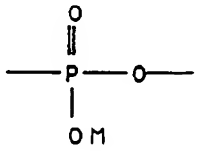


worin sind
R^1 ein Wasserstoffatom, eine Hydroxy-, Mercapto- oder Aminogruppe;
R^2 ein Wasserstoffatom, eine Hydroxygruppe, ein Fluor-, Chloratom oder eine Aminogruppe;
R^3 und R^4 unabhängig voneinander ausgewählt aus



Amino-, Hydroxy- oder einem Etherrest, der definiert ist als OR^5, worin R^5 ein C_{1-6}-Alkyl, ein Arylalkyl, das wahlweise mit ein oder mehreren Alkoxy-, Amino-, Nitril- oder Sulphonamidgruppen oder ein oder mehreren Halogenatomen substituiert sind oder einem Esterrest, der abgeleitet ist aus der Carbonsäure R^6COOH, dem Kohlensäureester R^7OCOOH, dem zweifachen Kohlensäureester $R^7COOCH(R^8)OCOOH$, der Sulphonsäure

R^7SO_2OH, der Carbaminsäure $R^7NHCOOH$ oder eine Phosphorsäure, worin sind: R^6 ein Wasserstoffatom, C_{1-17}-Alkyl, ein Alkoxyalkyl, ein Arylalkyl oder Aryl ist, wobei R^7 ein C_{1-17}-Alkyl, Arylalkyl oder Aryl ist, R^8 ein Wasserstoffatom oder ein C_{1-3}-Alkyl ist und die besagten Aryl- und Arylalkylgruppen substituiert sein können mit ein oder mehreren Alkyl-, Alkoxy-, Amino-, Nitril-, Sulphonamidgruppen oder ein oder mehreren Halogenatomen oder R^3 zusammen mit R^4 ein



worin M ein Wasserstoffatom oder ein pharmazeutisch akzeptables Gegenion ist; und n gleich 1 oder 2 ist; und pharmazeutisch akzeptable Salze davon, zur Herstellung eines Medikaments zur therapeutischen und/oder prophylaktischen Behandlung des erworbenen Immunschwäche-Syndroms und von Infektionen aufgrund von Viren, die zur Replikation reverse Transkriptase benötigen.

11. Verwendung einer Verbindung der Formel gemäß Anspruch 10, in Form eines optischen Isomers.

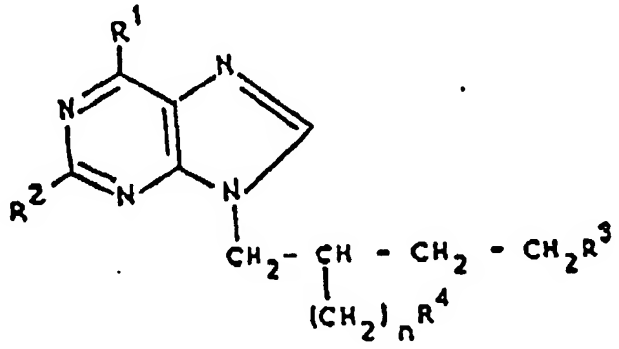
12. Verwendung gemäß Aspruch 10 oder 11 zur Behandlung von Infektionen aufgrund von HIV-Viren.

13. Verwendung gemäß Anspruch 10 oder 11 zur Behandlung von Infektionen aufgrund von Hepatis-B-Viren.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule I:



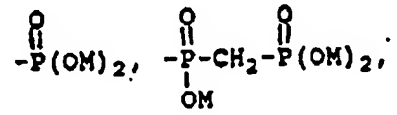
I

dans laquelle:

R^1 est un atome d'hydrogène, un groupe hydroxy, mercapto ou amino;

R^2 est un atome d'hydrogène, de fluor, de chlore, un groupe hydroxy ou amino;

R^3 et R^4 sont indépendamment choisis parmi



amino, hydroxy,

ou un résidu éther de ceux-ci défini en tant que OR^5, dans lequel R^5 est un groupe alkyle en C_{1-6}, arylalkyle éventuellement substitué avec un ou plusieurs groupes alcoxy, amino, nitrile ou sulfonamido ou un ou plusieurs atomes d'halogènes, ou un résidu ester de ceux-ci dérivé d'un acide carboxylique R^6COOH, d'un acide car-

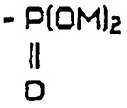
bonique R^7OCOOH, d'un ester double d'un acide carbonique $R^7CO_2CH(R^8)OCO_2H$, d'un acide sulfonique R^7SO_2OH, d'un acide carbamique $R^7NHCOOH$ ou d'un acide phosphorique, dans lesquels R^6 est un atome d'hydrogène, un groupe alkyle en C_{1-17}, alcoxyalkyle ou aryle, R^7 est un groupe alkyle en C_{1-17}, arylalkyle ou aryle, R^8 est un atome d'hydrogène ou un groupe alkyle en C_{1-13} et ces groupes aryles et arylalkyles peuvent éventuellement être substitués avec un ou plusieurs groupes alkyle, alcoxy, nitrile ou sulfonamide ou un ou plusieurs atomes d'halogène,
ou R^3 forme avec R^4 un groupe

dans lequel
M est un atome d'hydrogène ou un contre-ion acceptable du point de vu pharmaceutique;
et n est 1 ou 2; à condition que, lorsque R^2 est un groupe amino et que R^3 et R^4 sont un groupe hydroxy, R^1 ne soit pas un groupe hydroxy et que de plus, lorsque n = 1, R^1 ne soit pas un atome d'hydrogène, et des sels de celui-ci acceptables du point de vue pharmaceutique.

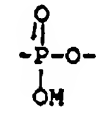
2. Composé suivant la revendication 1 sous la forme d'un isomère optique.

3. Composé suivant la revendication 1 ou la revendication 2, dans lequel R^3 et R^4 sont tous les deux un groupe hydroxy.

4. Composé suivant la revendication 1 ou la revendication 2, dans lequel R^3 est



et R^4 est OH,
ou R^3 forme avec R^4 un groupe



5. Composé suivant l'une quelconque des revendication 1 à 4, pour l'utilisation en thérapie.

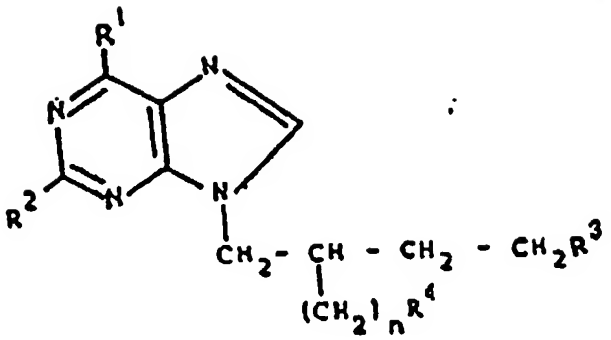
6. Composé de formule I suivant l'une quelconque des revendications 1 à 4, pour l'utilisation dans le traitement thérapeutique et/ou prophylactique des infections virales chez un hôte animal ou humain nécessitant un traitement.

7. Composé suivant la revendication 6 pour le traitement d'infections provoquées par les virus de l'herpès.

8. Composé suivant la revendication 6 pour le traitement d'infections provoquées par des virus nécessitant une reverse transcriptase pour leur réplication, comprenant les virus d'immunodéficience humaine et le virus de l'hépatite B.

9. Composition pharmaceutique comprenant en tant que composant actif, un composé suivant l'une quelconque des revendications 1 à 4 et un support acceptable du point de vue pharmaceutique.

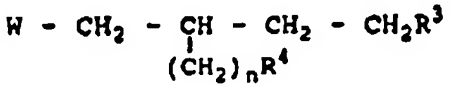
10. Procédé pour la préparation d'un composé de formule I



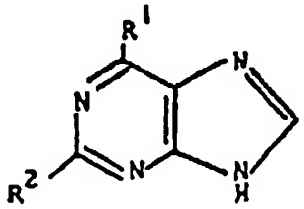
I

dans laquelle R^1, R^2, R^3, R^4, R^5 et n sont tels que définis dans la revendication 1, par

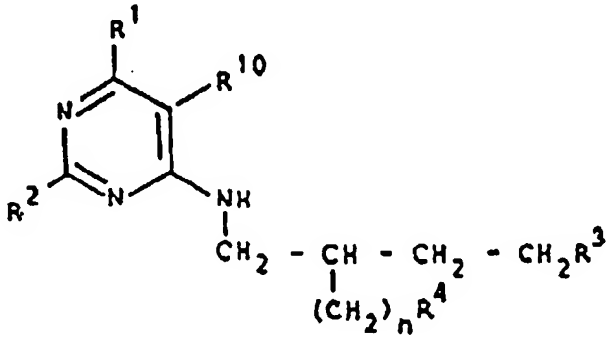
A. condensation d'une chaîne latérale acyclique



dans laquelle W est un groupe terminal mobile, en position N-9 d'un dérivé de la purine

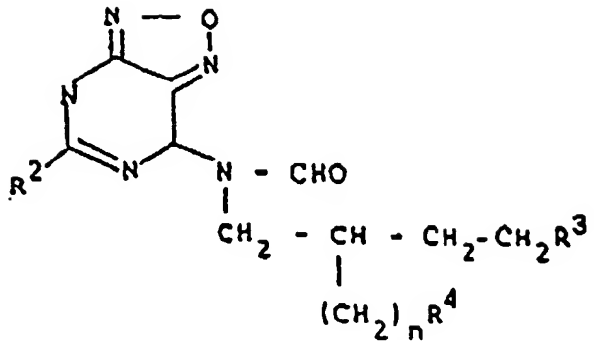


B. fermeture du cycle imidazole d'un dérivé de pyrimidine de formule



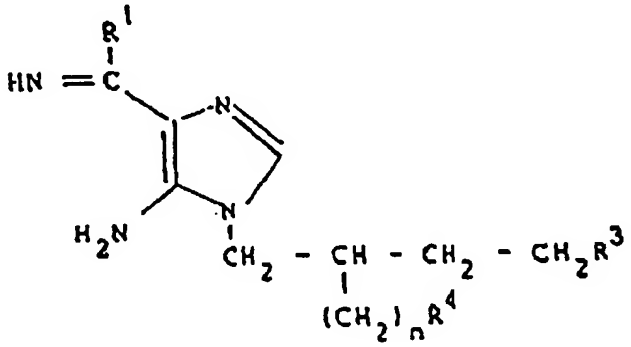
dans laquelle R^{10} est un groupe amino ou un dérivé amino;

C. fermeture du cycle imidazole d'un noyau furazano-[3,4-d]pyrimidine de formule



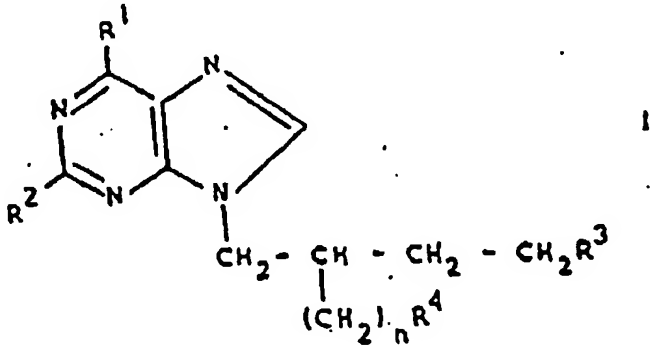
et coupure réductrice du noyau en un composé de formule I, dans laquelle R^1 est un groupe amino; ou

D. fermeture du cycle pyrimidine d'un dérivé imidazole de formule



dans lesquels procédés, R^1 à R^4 et n sont tels que définis dans la revendication 1 et peuvent être éventuellement protégés par des groupes protecteurs convenables, de façon à fournir un mélange d'isomères optiques ou un isomère optique unique, le mélange racémique obtenu pouvant être éventuellement séparé en isomères optiques.

11. Utilisation de'un composé de formule I :



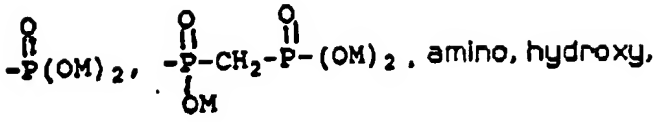
I

dans laquelle:

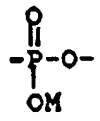
R^1 est un atome d'hydrogène, un groupe hydroxy, mercapto ou amino;

R^2 est un atome d'hydrogène, de fluor, de chlore, un groupe hydroxy ou amino;

R^3 et R^4 sont indépendamment choisis parmi



amino, hydroxy,
ou un résidu éther de ceux-ci défini en tant que OR^5, dans lequel R^5 est un groupe alkyle en C_{1-8}, arylalkyle éventuellement substitué avec un ou plusieurs groupes alcoxy, amino, nitrile ou sulfonamido ou un ou plusieurs atomes d'halogènes, ou un résidu ester de ceux-ci dérivé d'un acide carboxylique R^6COOH, d'un acide carbonique R^7OCOOH, d'un ester double d'un acide carbonique $R^7CO_2CH(R^8)OCO_2H$, d'un acide sulfonique R^7SO_2OH, d'un acide carbamique $R^7NHCOOH$, ou d'un acide phosphorique, dans lesquels R^6 est un atome d'hydrogène, un groupe alkyle en C_{1-17}, alcoxyalkyle, arylalkyle ou aryle, R^7 est un groupe alkyle en C_{1-17}, arylalkyle ou aryle, R^8 est un atome d'hydrogène ou un groupe alkyle en C_{1-13} et ces groupes aryles et arylalkyles peuvent éventuellement être substitués avec un ou plusieurs groupes alkyle, alcoxy, amino, nitrile, ou sulfonamide ou un ou plusieurs atomes d'halogène,
ou R^3 forme avec R^4 un groupe



dans lequel
M est un atome d'hydrogène ou un contre-ion acceptable du point de vue pharmaceutique;
et n est 1 ou 2; et des sels de celui-ci acceptables du point de vue pharmaceutique pour la fabrication d'un médicament pour un traitement thérapeutique et/ou prophylactique du syndrome immunodéficitaire acquis et d'infections provoquées par des virus requérant une reverse transcriptase pour leur réplication.

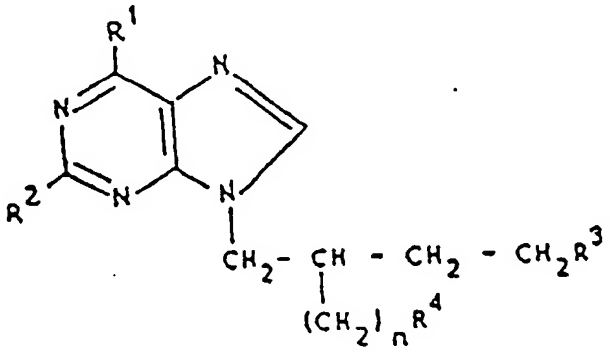
12. Utilisation d'un composé de formule suivant la revendication 11 sous la forme d'un isomère optique.

13. Utilisation suivant la revendication 11 ou la revendication 12 pour le traitement des infections provoquées par des virus HIV.

14. Utilisation suivant la revendication 11 ou la revendication 12 pour le traitement des infections provoquées par des virus de l'hépatite B.

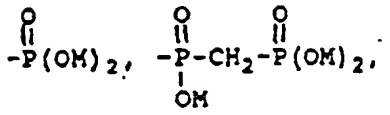
Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un composé de formule I

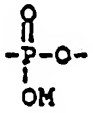


I

dans laquelle :
R^1 est un composé d'hydrogène, un groupe hydroxy, mercapto ou amino;
R^2 est un atome d'hydrogène, de fluor, de chlore, un groupe hydroxy ou amino;
R^3 et R^4 sont indépendamment choisis parmi

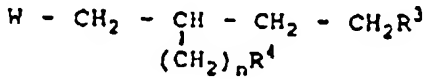


amino, hydroxy,
ou un résidu éther de ceux-ci défini en tant que OR^5, dans lequel R^5 est un groupe alkyle en C_{1-6}, arylalkyle éventuellement substitué avec un ou plusieurs groupes alcoxy, amino, nitrile ou sulfonamido ou un ou plusieurs atomes d'halogène, ou un résidu ester de ceux-ci dérivé d'un acide carboxylique R^6COOH, d'un acide carbonique R^7OCOOH, d'un ester double d'un acide carbonique $R^7CO_2CH(R^8)OCO_2H$, d'un acide sulfonique R^7SO_2OH, d'un acide carbamique $R^7NHCOOH$ d'un acide phosphorique, dans lesquels R^6 est un atome d'hydrogène, un groupe alkyle en C_{1-17}, alcoxyalkyle, arylalkyle ou aryle, R^7 est un groupe alkyle en C_{1-17}, arylalkyle ou aryle, R^8 est un atome d'hydrogène ou un groupe alkyle en C_{1-13} et ces groupes aryles et arylalkyles peuvent éventuellement être substitués avec un ou plusieurs groupes alkyle, alcoxy, amino, nitrile ou sulfonamide ou un ou plusieurs atomes d'halogène,
ou R^3 forme avec R^4 un groupe

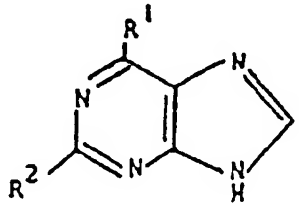


dans lequel
M est un atome d'hydrogène ou un contre-ion acceptable du point de vue pharmaceutique;
et n est 1 ou 2; à condition que, lorsque R^2 est un groupe amino et que R^3 et R^4 sont un groupe hydroxy, R^1 ne soit pas un groupe hydroxy et que de plus, lorsque n = 1, R^1 ne soit pas un atome d'hydrogène, et des sels de celui-ci acceptables du point de vue pharmaceutique, par

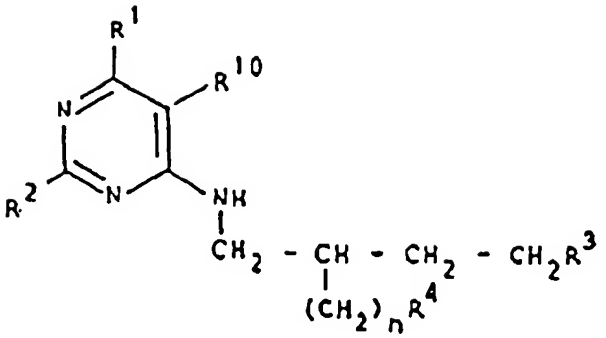
A. condensation d'une chaîne latérale acyclique



dans laquelle W est un groupe terminal mobile, en position N-9 d'un dérivé de la purine

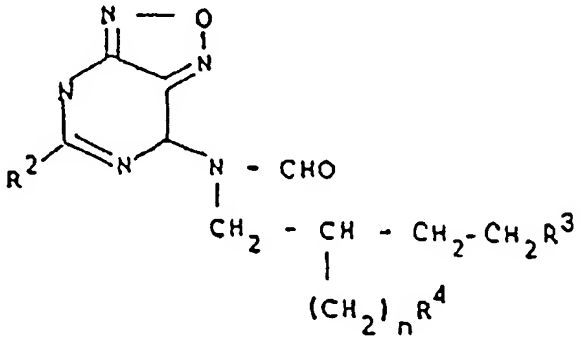


B. fermeture du cycle imidazole d'un dérivé de pyrimidine de formule



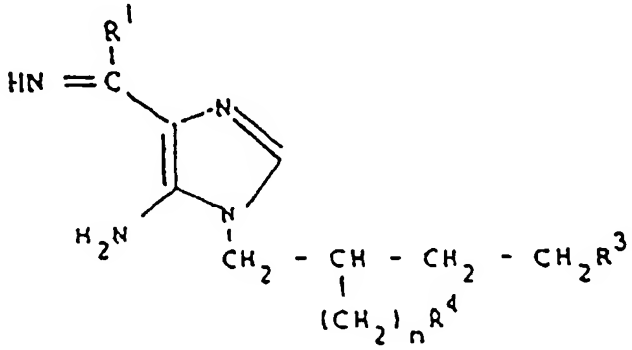
dans laquelle R^{10} est un groupe amino ou un dérivé amino;

C. fermeture du cycle imidazole d'un noyau furazano-[3,4-d] pyrimidine de formule



et coupure réductrice du noyau furazane en un composé de formule I, dans laquelle R^1 est un groupe amino; ou

D. fermeture du cycle pyrimidine d'un dérivé imidazole de formule

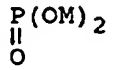


dans lesquels procédés, R^1 à R^4 et n sont tels que définis dans la revendication 1 et peuvent être éventuellement protégés par des groupes protecteurs convenables, de façon à fournir un mélange d'isomères optiques ou un isomère optique unique, le mélange racémique obtenu pouvant être éventuellement séparé en isomères optiques.

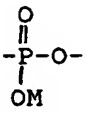
2. Procédé suivant la revendication 1 pour la préparation d'un composé de formule I sous la forme d'un isomère optique.

3. Procédé suivant la revendication 1 ou la revendication 2 pour la préparation d'un composé de formule I, dans lequel R^3 et R^4 sont tous les deux un groupe hydroxy.

4. Procédé suivant la revendication 1 ou la revendication 2 pour la préparation d'un composé de formule I, dans lequel R^3 est



et R^4 est OH,
ou R^3 forme avec R^4 un groupe



5. Procédé suivant l'une quelconque des revendications 1 à 4, pour utilisation en thérapie.

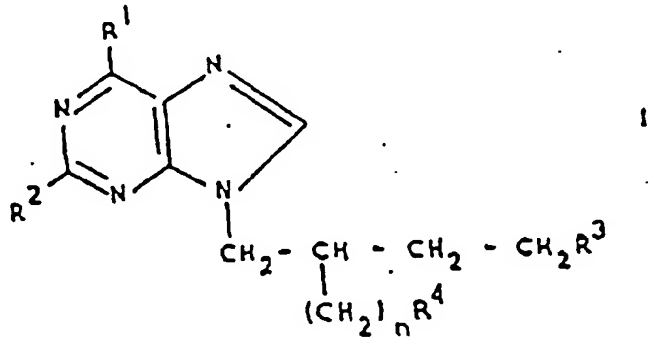
6. Procédé pour la préparation d'un composé de formule I suivant l'une quelconque des revendications 1 à 4, pour le traitement thérapeutique et/ou prophylactique des infections virales chez un hôte animal ou humain nécessitant un traitement.

7. Procédé pour la préparation d'un composé suivant la revendication 6 pour le traitement d'infections provoquées par les virus de l'herpès.

8. Procédé pour la préparation d'un composé suivant la revendication 6 pour le traitement d'infections provoquées par des virus nécessitant une reverse transcriptase pour leur réplication, comprenant les virus d'immunodéficience humaine et le virus de l'hépatite B.

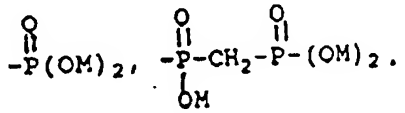
9. Procédé pour la préparation d'une composition pharmaceutique comprenant la combinaison, en tant que composant actif, d'un composé suivant l'une quelconque des revendications 1 à 4 et d'un support acceptable du point de vue pharmaceutique.

10. Utilisation d'un composé de formule I:



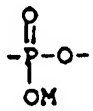
I

dans laquelle:
R^1 est un atome d'hydrogène, un groupe hydroxy, mercapto ou amino:
R^2 est un atome d'hydrogène, de fluor, de chlore, un groupe hydroxy ou amino;
R^3 et R^4 sont indépendamment choisis parmi



amino, hydroxy,
ou un résidu éther de ceux-ci défini en tant que OR^5, dans lequel R^5 est un groupe alkyle en C_{1-6}, arylalkyle éventuellement substitué avec un ou plusieurs groupes alcoxy, amino, nitrile ou sulfonamido ou un ou plusieurs atomes d'halogène, ou un résidu ester de ceux-ci dérivé d'un acide carboxylique R^8COOH, d'un acide carbonique R^7OCOOH, d'un ester double d'un acide carbonique $R^7CO_2CH(R^8)OCO_2H$, d'un acide sulfonique R^7SO_2OH, d'un acide carbamique $R^7NHCOOH$ ou d'un acide phosphorique, dans lesquels R^6 est un atome

d'hydrogène, un groupe alkyle en C_{1-17}, alcoxyalkyle, arylalkyle ou aryle, R^7 est un groupe alkyle en C_{1-17}, arylalkyle ou aryle, R^8 est un atome d'hydrogène ou un groupe alkyle en C_{1-13} et ces groupes aryles et arylalkyles peuvent éventuellement être substitués avec un ou plusieurs groupes alkyle, alcoxy, amino, nitrile ou sulfonamide ou un ou plusieurs atomes d'halogène,
ou R^3 forme avec R^4 un groupe



dans lequel
M est un atome d'hydrogène ou un contre-ion acceptable du point de vue pharmaceutique;
et n est 1 ou 2; et des sels de celui-ci acceptables du point de vue pharmaceutique pour la fabrication d'un médicament pour un traitement thrapeutique et/ou prophylactique du syndrome immunodéficitaire acquis et d'infections provoquées par des virus requérant une reverse transcriptase pour leur réplication.

11. Utilisation d'un composé de formule suivant la revendication 10 sous la forme d'un isomère optique.

12. Utilisation suivant la revendication 10 ou la revendication 11 pour le traitement des infections provoquées par des virus HIV.

13. Utilisation suivant la revendication 10 ou la revendication 11 pour le traitement des infections provoquées par des virus de l'hépatite B.

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(54) Antiviral pyrimidine and purine compounds, process for their preparation and pharmaceutical compositions containing them.

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EP-A- 0 072 027
EP-A- 0 099 493
EP-A- 0 308 065

JOURNAL OF MEDICINAL CHEMISTRY, vol. 26, no. 4, April 1983, pages 602-604, American Chemical Society, Columbus, Ohio, US; L. COLLA et al.: "Synthesis and antiviral activity of water-soluble esters of acyclovir [9-[(2-hydroxyethoxy)methyl]guanine]"

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EP 0 375 329 B1

Description

The present invention relates to novel antiviral esters of pyrimidine and purine nucleosides containing an acyclic side chain.

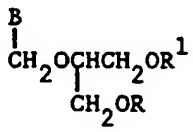
European Patent Specification 167385A describes and claims the antiviral pyrimidine nucleoside 1-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]cytosine and its physiologically acceptable salts and esters. The parent compound has been found to have particularly potent activity against cytomegalovirus (CMV) and Epstein-Barr virus (EBV).

The compound 9-[(2-hydroxy-1-hydroxymethylethoxy)methyl]guanine, which has the approved name ganciclovir, is described in UK Patent Specification 2104070A which also describes generally the pharmaceutically acceptable salts and certain esters of ganciclovir. Ganciclovir has been found to have potent activity against viruses of the herpes family particularly herpes simplex and cytomegalovirus. Ganciclovir has however, low oral bioavailability and is typically administered as a 1-hour intravenous infusion every 12 hours.

The 6-deoxy and 6-amino analogues of ganciclovir have also been described in the literature, the former being described in UK Patent Specification 2104070A and the latter in UK Patent Specification 2130204A.

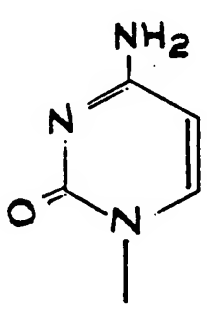
We have now found that valine amino acid esters of the compounds referred to above surprisingly have advantageous bioavailability when administered by the oral route, resulting in exceptionally high levels of the parent compound in the body. This enables less drug to be administered while still providing equivalent drug levels of the parent compound in the plasma. Oral administration means patient compliance is considerably simplified.

According to one feature of the present invention there is provided a compound of formula I:-

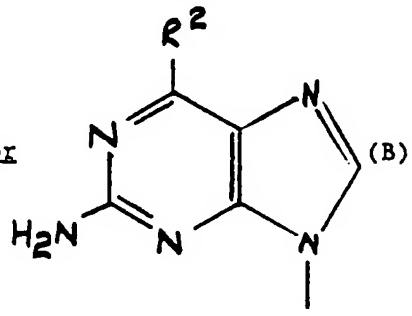


(I)

(wherein R and R^1 are independently selected from a hydrogen atom or a valine residue providing at least one of R and R^1 represents a valine residue and B represents a group of formula



(A) or



(B)

in which R^2 represents a C_{1-6} straight chain, C_{3-6} branched chain or C_{3-6} cyclic alkoxy group, or a hydroxy or an amino group) and the physiologically acceptable salts thereof.

A group falling within formula (I) above is where R^2 represents a hydroxy or an amino group.

It will be appreciated that the compound of formula (I) in which B represents a group of formula (B) wherein R^2 represents hydroxy is shown in the enol tautomeric form. The compound may also exist in its keto tautomeric form.

Among the above amino acid esters of formula (I) those of cytosine and ganciclovir are particularly preferred by virtue of their especially improved bioavailability in comparison with the parent compounds.

The valine amino acid esters according to the invention includes the mono- and di-esters of the compound of formula (I). The amino acids may be D-, L-and DL amino acids, with the L-amino acids being most preferred.

Examples of preferred compounds of formula (I) above include those of Examples 1 and 2.

The above-mentioned physiologically acceptable salts are preferably acid addition salts derived from an appropriate acid, e.g., hydrochloric, sulphuric, phosphoric, maleic, fumaric, citric, tartaric, lactic or acetic acid.

The above-defined valine amino acid esters of formula (I) and their salts which are hereinafter referred to as the compounds according to the invention, are especially useful for the treatment or prophylaxis of virus infections, especially herpes infections such as herpes simplex, varicella zoster, Epstein-Barr virus (human herpes virus-6 infections), and particularly cytomegalovirus, in humans or non-human animals. Examples of clinical conditions which are caused by such viruses include herpetic keratitis, herpetic encephalitis, cold sores and genital infections (caused by herpes simplex), chicken pox and shingles (caused by varicella zoster) and CMV-pneumonia and -retinitis, particularly in immunocompromised patients including renal and bone marrow transplant patients and patients with Acquired Immune Deficiency Syndrome (AIDS). Epstein-Barr virus (EBV) causes infectious mononucleosis, and is also suggested as the causative agent of nasopharyngeal cancer, immunoblastic lymphoma, Burkitt's lymphoma and hairy leukoplakia.

According to further features of the present invention we provide :

a) the compounds according to the invention for use in medical therapy particularly for the treatment or prophylaxis of viral infections, e.g., those referred to above;

b) the use of the compounds according to the invention for the manufacture of a medicament for the treatment or prophylaxis of viral infections, e.g., those referred to above.

The compounds according to the invention may be administered for therapy by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, intraocular and epidural). It will be appreciated that the preferred route may vary with for example the condition of the recipient.

For each of the above-indicated utilities and indications the amount required of the compound according to the invention will depend upon a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician. In general however, for each of these utilities and indications, a suitable, effective dose will be in the range 0.1 to 250mg per kilogram bodyweight of recipient per day, preferably in the range 1 to 100mg per kilogram bodyweight per day and most preferably in the range 5 to 20mg per kilogram bodyweight per day; an optimum dose is about 10mg per kilogram bodyweight per day. The desired dose is preferably presented as two, three, four or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1000mg, preferably 20 to 500mg and most preferably 100 to 400mg of the compound according to the invention per unit dosage form.

The compounds of the invention may be administered for the treatment or prophylaxis of viral infections alone or in combination with other therapeutic agents, for example, with other antiviral agents such as 9-(2-hydroxy-ethoxymethyl)guanine (acyclovir) used to treat herpes viral infections in particular HSV; with 3'-deoxy-3'-azidothymidine (zidovudine) or a 2',3'-dideoxynucleoside for example 2',3'-dideoxy cytidine, 2',3'-dideoxyinosine, 2',3'-dideoxyadenosine or 2',3'-dideoxyguanosine, used to treat retroviral infections in particular Human Immunodeficiency Virus (HIV) infections, interferons particularly α-interferon and soluble proteins such as CD4, or any other agents such as analagesics or antipyretics which when in combination with a compound of the invention provide a beneficial therapeutic effect.

While it is possible for the active ingredients to be administered alone it is preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the present invention comprise at least one compound according to the invention (also referred to hereafter as "the active ingredient"), together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutanous, intramuscular, intravenous, intradermal, intrathecal, intraocular and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers of finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

For infections of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient in an amount of, for example, 0.075 to 20% w/w, preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl-sulphoxide and related analogues.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerine, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Formulations for intramuscular administration are particularly preferred.

Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

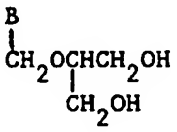
The present invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

For oral administration the compositions can be in the form of a tablet, granule, drench, paste, cachet, capsule or feed supplement. Granules may be made by the well known techniques of wet granulation, precompression or slugging. They can be administered to animals in an inert liquid vehicle so as to form a drench, or in a suspension with water or oil base. Preferably further accessory ingredients such as a dispersing agent are included. These formulations preferably contain from 15 to 85% of the active ingredient.

The compounds according to the invention may be prepared in conventional manner, e.g. by a process as described below.

Thus, according to a further feature of the present invention we provide a process for the preparation of the compounds according to the invention which comprises reacting the compound of formula (II)



(II)

(wherein B is as hereinbefore defined) with an optionally protected valine amino acid or functional equivalent thereof and optionally effecting one or more of the following conversions:-

i) removal of any protecting groups;

ii) where the resulting product is a compound of formula (I), conversion of the said compound into a physiologically acceptable salt thereof; and

iii) where the resulting product is a physiologically acceptable salt of a compound of formula (I), conversion of the said salt into the parent compound.

In the above process, the reaction may be carried out in a conventional manner, for example in a solvent such as pyridine, dimethylformamide etc., in the presence of a coupling agent such as N,N - dicyclohexylcarbodiimide, optionally in the presence of a catalytic base such as 4-dimethylaminopyridine. The water formed during the reaction may, if desired, be removed in conventional manner, for example by distillation or by the addition of a water-binding substance. Subsequently, the ester obtained as reaction product may be isolated in conventional manner.

As an alternative to the use of the valine amino acid per se, a functional equivalent of the acid may be employed, e.g., an acid halide such as the acid chloride, or an acid anhydride.

In order to avoid undesirable side-reactions, it may be advantageous to use an amino-protected derivative, examples of preferred amino-protecting groups including acyl, e.g., C_{1-4}alkanoyl such as acetyl; arylalkyloxycarbonyl, e.g., benzyloxycarbonyl; or aminoprecursor groups such as azido groups. It is particularly preferred to employ an amino acid protected by a benzyloxycarbonyl group. Such benzyloxycarbonyl protected compounds are commercially available, e.g., from Sigma Chemical Co., USA, or may be prepared by treating the appropriate amino acid with carbobenzoxy chloride in alkaline solution.

The optional conversions i), ii) and iii) may be effected in a conventional manner. Thus, for example, removal of protecting groups in conversion i) may be effected by hydrogenolysis or as appropriate. With regard to removal of protecting groups on the amino acid acyl radicals, hydrogenolysis, e.g., of arylalkyloxycarbonyl protecting groups, and conversion of azido group, e.g., by catalytic hydrogenation, e.g., using a palladium catalyst, are preferred.

The conversion of an amino acid ester into a physiologically acceptable salt may be effected in conventional manner, e.g., by treatment of the compound with an appropriate acid to form an acid addition salt.

Similarly, conversion of a salt into the parent amino acid ester may be effected in conventional manner for example, by treatment with a stoichiometric amount of an ion exchange resin (basic form), filtration to remove the resin and lyophilisation of the resulting solution.

The following Examples illustrate the present invention.

Example 1

a) 2-((4-(N-((benzyloxy)carbonyl)-L-valinamido)-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate) and 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate)

A suspension of 2 g of 4-amino-1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-2(1H)-pyrimidinone in 40 mL dry dimethylformamide (DMF) was slightly warmed until a clear solution remained. 5.84g of CBz-L-valine, 567 mg of dimethylaminopyridine (DMAP) and 4.79 g of dicylohexylcarbodiimide (DCC) was successively added. A white precipitate was observed after 15 min. The mixture was stirred at room temperature for 4 h. The resulting suspension was filtered and the filtrate distributed between water and CH_2Cl_2. The organic fraction was dried ($MgSO_4$), filtered and evaporated in vacuo to a yellow oil. The oil was purified by flash chromatography of silica gel. Eluting with 2% methanol in dichloromethane afforded the triacylated derivative, 1.12 g (13%) as a white foam.

Eluting with 4% methanol in dichloromethane afforded the N,O,O-triacylated derivative, 113 mg (2%).

Eluting with 10% methanol in dichloromethane afforded the O,O-diacylated derivative, 3.44 g (54%) as a white foam.

b) 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-pronanediyl bis(L-valinate)

To a cool mixture of 3.44 g of 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate) and 7g of 10% palladium catalyst in acetic acid was slowly added 8.65 mL of 1,4-cyclohexadiene. The mixture was allowed to stir at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite. The filtrate was then concentrated and dried in the lyophilizer for 48 h. The resulting beige foam was scraped off affording 2.38 g (68%, as the acetic acid salt) of the title compound. The elemental analysis (showing 2M of acetic acid and 1M of water) UV, ^1H, ^{13}C-NMR spectra were consistent with the title structure.

Example 2

2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(L-valinate)

a) 2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate)

A solution of 22.5g(0.09M) of N-benzyloxycarbonyl chloride (Sigma Chemical Co.) L.valine, 18.6g (0.09mol) of N,N-dicyclohexylcarbodiimide and 1.2g (0.01mol) of 4-dimethylaminopyridine in 100mL of dimethylformamide was stirred under nitrogen for 10 minutes. After the addition of 20mL more of dimethylformamide and 7.65g (0.03mol) of 9-(1,3-dihydroxypropoxymethyl)guanine, the mixture was stirred for 18 hours at ambient temperature.

The suspension was filtered, washing the precipitate with dichloromethane and the combined filtrate and washings were evaporated in vacuo. The residual yellow oil was dissolved in methanol and absorbed on silica gel. The mixture was evaporated in vacuo and the powdery residue added to a column prepared for flash chromatography. The column was eluted first with 2% methanol in dichloromethane to remove an impurity and the desired product was then eluted off with 5% methanol in dichloromethane. Evaporation of this eluate gave 14.3g (66%) of 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis (N-((benzyloxy)carbonyl)-L-valinate), which gave a satisfactory elemental analysis, ^1H HMR and ^{13}C spectra.

b) 2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-pronanediyl bis(L-valinate)

A mixture of 0.722g (1.0mmol) of 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate) and 300mg of 10% palladium on carbon in 10mL of acetic acid was shaken in a Parr apparatus at ambient temperature at an initial pressure of 50 psi for 18 hours. The mixture was filtered through a pad of celite, washing the pad with acetic acid. The filtrate was evaporated at room temperature under pump vacuum giving a syrup (822mg) which was dried at 100 °C with 1.0mm pressure. The resulting glass turned to a solid on scraping with a spatula and was the desired 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(L-valinate). The compound gave satisfactory ^1H NMR, ^{13}C, UV and Mass spectra. It analyzed for 2 moles of acetic acid and 0.05 moles of water.

The following Examples, 3 to 5, illustrate pharmaceutical formulations according to the invention where the active ingredient is a compound according to the invention.

Example 3

Tablet

Active compound	200mg
Lactose	235mg
Starch	50mg
Polyvinylpyrrolidone	50mg
Magnesium stearate	5mg

Mix the active compound with the lactose and starch and wet granulate with a solution of the polyvinylpyrrolidone. Dry, sift, blend the granules with magnesium stearate and compress.

Example 4

Capsule

Active compound	200mg
Lactose	184mg
Sodium starch glycollate	8mg
Polyvinylpyrrolidone	6mg
Magnesium stearate	2mg

Mix the active compound with the lactose and sodium starch glycollate and wet granulate with a solution of the polyvinylpyrrolidone. Dry, sift, blend the granules with the magnesium stearate and fill into hard gelatin capsules.

Example 5

Intravenous Injections

A)	Active compound	200mg
	Sodium hydroxide solution	q.s. to pH 7.0 to 7.5
	Water for injections to	5.0ml

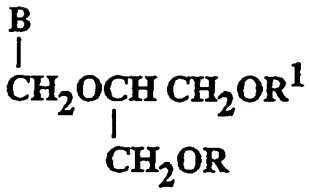
Dissolve the active compound in part of the water for injections. Adjust the pH with the sodium hydroxide solution and make up to volume with additional water for injections. Under aseptic conditions, sterilise the solution by filtration, fill into sterile ampoules and seal the ampoules.

B)	Active compound	100mg
	Sodium hydroxide solution	q.s. to pH 7.0 to 7.5
	Mannitol	125mg
	Water for injections to	2.5ml

Dissolve the active compound and mannitol in part of the water for injections. Adjust the pH with the sodium hydroxide solution and make up to volume with additional water for injections. Under aseptic conditions, sterilise the solution by filtration, fill into sterile vials and remove the water by freeze-drying. Seal the vials under an atmosphere of nitrogen and close with a sterile stopper and aluminium collar.

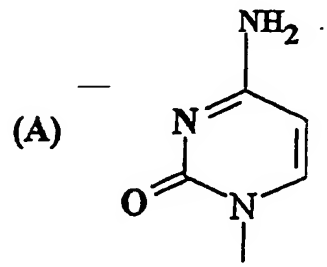
Claims

1. A compound of formula (I):



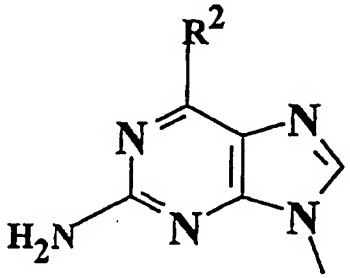
(I)

(wherein R and R^1 are independently selected from a hydrogen atom or a valine residue providing at least one of R and R^1 represents a valine residue and B represents a group of formula



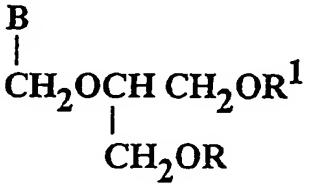
(A)

or (B)



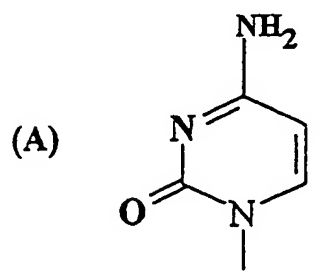
in which R^2 represents a C_{1-6} straight chain, C_{3-6} branched chain or C_{3-6} cyclic alkoxy group or a hydroxy or an amino group) and physiologically acceptable salts thereof.

2. A compound of formula (I):



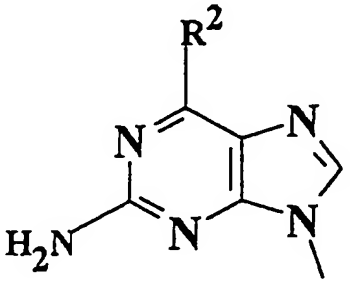
(I)

(wherein R and R^1 are independently selected from a hydrogen atom or a valine residue providing at least one of R and R^1 represents a valine residue and B represents a group of formula



(A)

or (B)



in which R^2 represents a hydroxy or an amino group and physiologically acceptable salts thereof.

3. A compound of formula (I) 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-propanediyl bis (L-valinate).

4. A compound of formula (I) 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis (L-valinate).

5. A compound of formula (I) as claimed in claims 1 or 2 in which all valine groups are in the L-form.

6. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof for use in medical therapy.

7. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof for use in the treatment or prophylaxis of viral infections.

8. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof for use in the treatment or prophylaxis of herpes virus infections.

9. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof for use in the treatment or prophylaxis of a cytomegalovirus infection.

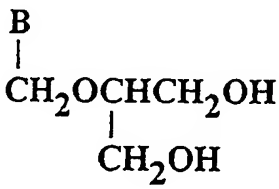
10. Use of a compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof in the manufacture of a medicament for the treatment or prophylaxis of viral infections.

11. A pharmaceutical formulation comprising as active ingredient a compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 or a physiologically acceptable salt thereof together with at least one pharmaceutically acceptable carrier therefor.

12. A pharmaceutical formulation as claimed in claim 11 adapted for oral or parenteral administration.

13. A pharmaceutical formulation as claimed in claim 11 in the form of a tablet or capsule.

14. A process for the preparation of a compound of formula (I) (as defined in claim 1) and physiologically acceptable salts thereof which comprises reacting a compound of formula (II)



(II)

(wherein B is as defined in claim 1) with an optionally protected valine or a functional equivalent thereof and optionally effecting one or more of the following conversions:

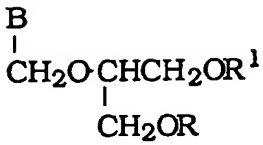
i) removal of any protecting groups;

ii) where the resulting product is a compound of formula (I), conversion of the said compound into a physiologically acceptable salt thereof; and

iii) where the resulting product is a physiologically acceptable salt of a compound of formula (I), conversion of the said salt into the parent compound.

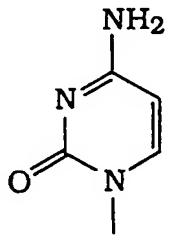
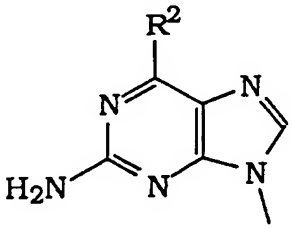
Patentansprüche

1. Verbindung der Formel (I):



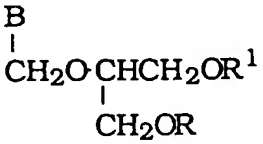
(I)

(worin R und R^1 unabhängig voneinander aus Wasserstoffatomen und Valin-Resten ausgewählt sind, mit der Maßgabe, daß mindestens einer der Reste R und R^1 einen Valin-Rest darstellt, und B eine Gruppe der Formel

(A)  oder (B) 

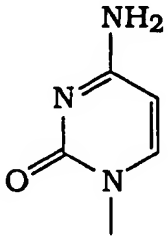
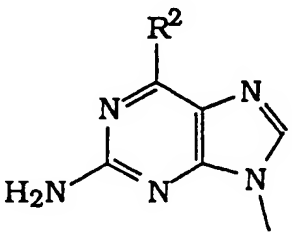
bedeuten,
worin R^2 eine geradkettige C_{1-6}-Alkoxygruppe, verzweigtkettige C_{3-6}-Alkoxygruppe, eine cyclische C_{3-6}-Alkoxygruppe, eine Hydroxylgruppe oder eine Aminogruppe darstellt) und deren physiologisch annehmbare Salze.

2. Verbindung der Formel (I):



(I)

(worin R und R^1 unabhängig voneinander aus Wasserstoffatomen und Valin-Resten ausgewählt sind, mit der Maßgabe, daß mindestens einer der Reste R und R^1 einen Valin-Rest darstellt, und B eine Gruppe der Formel

(A)  oder (B) 

bedeuten,
worin R^2 eine Hydroxylgruppe oder eine Aminogruppe darstellt) und deren physiologisch annehmbare Salze.

3. Verbindung der Formel (I), nämlich 2-((4-Amino-1,2-dihydro-2-oxo-1-pyrimidinyl)-methoxy)-1,3-propandiyl-bis(L-valinat).

4. Verbindung der Formel (I), nämlich 2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)-methoxy)-1,3-propandiyl-bis(L-valinat).

5. Verbindung der Formel (I) nach den Ansprüchen 1 oder 2, worin sämtliche Valin-Gruppen in der L-Form vorliegen.

6. Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und deren physiologisch annehmbare Salze zur Verwendung in der medizinischen Therapie.

7. Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und deren physiologisch annehmbare Salze zur Behandlung oder Prophylaxe von Virusinfektionen.

8. Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und deren physiologisch annehmbare Salze zur Verwendung bei der Behandlung oder Prophylaxe von Herpes-Virusinfektionen.

9. Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und deren physiologisch annehmbare Salze zur Verwendung bei der Behandlung oder Prophylaxe einer Cytomegalovirus-Infektion.

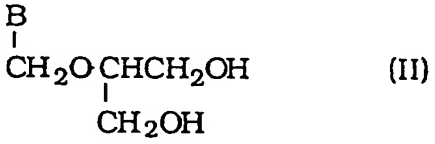
10. Verwendung einer Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und der physiologisch annehmbaren Salze davon bei der Herstellung eines Arzneimittels zur Behandlung oder Prophylaxe von Virusinfektionen.

11. Pharmazeutische Zubereitung enthaltend als Wirkstoff eine Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 oder ein physiologisch annehmbares Salz davon zusammen mit mindestens einem dafür geeigneten pharmazeutisch annehmbaren Trägermaterial.

12. Pharmazeutische Zubereitung nach Anspruch 11, die für die orale oder parenterale Verabreichung geeignet ist.

13. Pharmazeutische Zubereitung nach Anspruch 11, die in Form einer Tablette oder einer Kapsel vorliegt.

14. Verfahren zur Herstellung einer Verbindung der Formel (I) (wie sie in Anspruch 1 definiert ist) und von deren physiologisch annehmbaren Salzen, welches darin besteht, eine Verbindung der Formel (II)



(II)

(worin B die in Anspruch 1 angegebenen Bedeutungen besitzt) mit einem gegebenenfalls geschützten Valin oder einem funktionellen Äquivalent davon umzusetzen und gegebenenfalls eine oder mehrere der folgenden Umwandlungen zu bewirken:

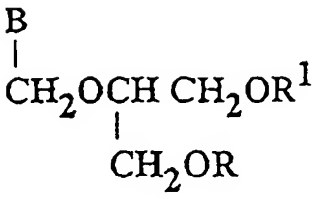
i) Abspaltung von eventuell vorhandenen Schutzgruppen;

ii) Umwandlung einer Verbindung der Formel (I) in ein physiologisch annehmbares Salze davon; und

iii) Umwandlung eines physiologisch annehmbaren Salzes einer Verbindung der Formel (I) in die Mutterverbindung.

Revendications

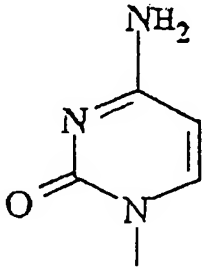
1. Composé de formule (I) :



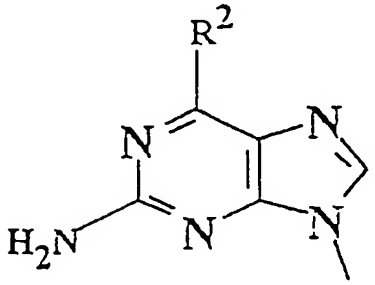
(I)

(dans laquelle R et R^1 sont choisis indépendamment parmi un atome d'hydrogène ou un résidu valine, à condition qu'au moins un des groupes R et R^1 représente un résidu valine et B représente un groupe de formule

(A)

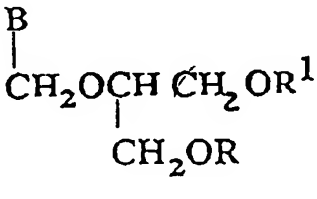


ou (B)



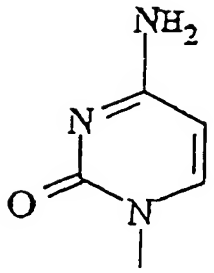
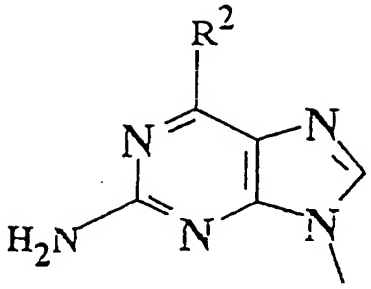
dans laquelle R^2 représente une chaîne droite en C_{1-6}, une chaîne ramifiée en C_{3-6} ou un groupe alkoxy cyclique en C_{3-6} ou un groupe hydroxy ou un groupe amino) et des sels physiologiquement acceptables de ceux-ci.

2. Composé de formule (I) :



(I)

(dans laquelle R et R^1 sont choisis indépendamment parmi un atome d'hydrogène ou un résidu valine à condition qu'au moins un des groupes R et R^1 représente un résidu valine et B représente un groupe de formule

(A)  ou (B) 

dans laquelle R^2 représente un groupe hydroxy ou un groupe amino et des sels physiologiquement acceptables de ceux-ci.

3. Composé de formule (I) 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)méthoxy)-1,3-propanediyl bis (L-valinate).

4. Compose de formule (I) 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)méthoxy)-1,3-propanediyl bis (L-valinate).

5. Composé de formule (I) tel que revendiqué dans les revendications 1 ou 2 dans lequel tous les groupes valine sont sous la forme L.

6. Composé de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci pour usage dans une thérapie médicale.

7. Compose de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci pour usage dans le traitement curatif ou préventif d'infections virales.

8. Composé de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci pour usage dans le traitement curatif ou préventif d'infections par le virus de l'herpès.

9. Composé de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci pour usage dans le traitement curatif ou préventif d'une infection par le cytomégalovirus.

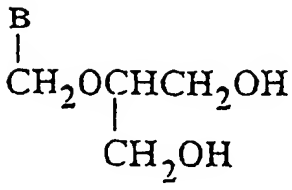
10. Utilisation d'un composé de formule (I) tel que revendique à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci dans la préparation d'un médicament pour le traitement curatif ou préventif d'infections virales.

11. Formulation pharmaceutique comprenant comme ingrédient actif un compose de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 ou des sels physiologiquement acceptables de celui-ci avec au moins un véhicule pharmaceutiquement acceptable pour celui-ci.

12. Formulation pharmaceutique telle que revendiquée à la revendication 11 adaptée à une administration par voie orale ou parentérale.

13. Formulation pharmaceutique telle que revendiquée à la revendication 11 sous la forme d'un comprimé ou d'une capsule.

14. Procédé pour la préparation d'un composé de formule (I) (tel que défini à la revendication 1) et des sels physiologiquement acceptables de celui-ci qui comprend une étape consistant à faire réagir un composé de formule (II)



(II)

(dans laquelle B est tel que défini à la revendication 1) avec un groupe valine éventuellement protégé ou un équivalent fonctionnel de celui-ci et, éventuellement une étape consistant à effectuer une ou plusieurs des conversions suivantes :

i) élimination de tous les groupes de protection ;

ii) lorsque le produit résultant est un composé de formule (I), conversion dudit composé en un sel physiologiquement acceptable de celui-ci ; et

iii) lorsque le produit résultant est un sel physiologiquement acceptable d'un compose de formule (I), conversion dudit sel en le compose de formule (I)